Castleman Disease

What is Castleman disease?

Castleman disease (CD) is a rare disease of lymph nodes and related tissues. It is also known as *Castleman's disease*, *giant lymph node hyperplasia*, and *angiofollicular lymph node hyperplasia* (AFH). It was first described by Dr. Benjamin Castleman in the 1950s.

CD is not cancer. Instead, it is called a *lymphoproliferative disorder*. This means there is an abnormal overgrowth of cells of the lymph system that is similar in many ways to lymphomas (cancers of lymph nodes).

Even though CD is not officially a cancer, one form of this disease (known as *multicentric Castleman disease*) acts very much like lymphoma. In fact, many people with this disease eventually develop lymphomas. And like lymphoma, CD is often treated with chemotherapy or radiation therapy. This is why it is included in the American Cancer Society's cancer information. (For information about lymphoma, see our documents *Hodgkin Disease* and *Non-Hodgkin Lymphoma*.)

About lymph nodes and lymphoid tissue

To understand Castleman disease, it helps to know about the body's lymph system.

Lymphoid tissue, also known as *lymphatic tissue*, is the main part of the immune system. It is formed by different types of cells that work together to help the body fight infections. The main cells in lymphoid tissue are lymphocytes, a type of white blood cell. There are 2 main types of lymphocytes: B cells and T cells.

Lymphoid tissue is found in many places throughout the body, including:

- **Lymph nodes:** bean-sized collections of lymphocytes found in small groups throughout the body, including inside the chest, abdomen, and pelvis. They can sometimes be felt under the skin in the neck, under the arms, and in the groin.
- **Thymus:** a small organ behind the upper part of the breastbone and in front of the heart. The thymus plays a vital role in development of T cells.

- **Spleen:** an organ under the lower part of the rib cage on the left side of the body. The spleen makes lymphocytes and other immune system cells to help fight infection. It also stores healthy blood cells and helps filter the blood.
- **Tonsils and adenoids:** collections of lymphoid tissue at the back of the throat. They help protect the body against germs that are breathed in or swallowed.
- **Bone marrow:** the soft inner part of certain bones that makes red blood cells, blood platelets, and white blood cells (including lymphocytes).
- **Digestive tract:** the stomach, intestines, and other organs, which also have lymphoid tissue.

Types of Castleman disease

Doctors can group CD in a number of ways, and they are still trying to determine which classification (or combination of them) provides the most helpful information.

Localized versus multicentric CD

The main way to classify CD is based on how much of the body it affects. The 2 main forms of CD are called *localized* and *multicentric*. They affect people very differently.

Localized (unicentric) Castleman disease

This is the more common type of CD. Localized CD only affects a single group of lymph nodes. It is not widespread. Lymph nodes in the chest or abdomen are affected most often. CD causes these lymph nodes to grow.

Enlarged lymph nodes in the chest can press on the windpipe (trachea) or smaller breathing tubes going into the lungs (bronchi), causing breathing problems. If the enlarged nodes are in the abdomen, the person might have pain, a feeling of fullness, or trouble eating. Sometimes the enlarged nodes are in places such as the neck, groin, or underarm area and are first noticed as a lump under the skin.

People with localized CD are usually cured when the affected lymph nodes are removed with surgery.

Multicentric Castleman disease

Multicentric Castleman disease (MCD) affects more than one group of lymph nodes. It can also affect other organs containing lymphoid tissue. This form sometimes occurs in people infected with human immunodeficiency virus (HIV), the virus that causes AIDS. Multicentric CD is more serious than the localized type, particularly in people with HIV infection. You can read more about HIV infection in our document *HIV, AIDS, and Cancer*.

People with MCD often have problems such as serious infections, fevers, weight loss, fatigue, night sweats, and nerve damage that can cause weakness and numbness. Blood

tests often show too few red blood cells (anemia) and high levels of antibodies in the blood (hypergammaglobulinemia).

MCD can weaken the body's immune system, making it hard to fight infection. Infections in people with MCD can be very serious, even life threatening. MCD also increases the risk of developing lymphoma, a cancer of lymphoid tissue, which can often be hard to treat.

Microscopic subtypes of CD

Castleman disease can also be classified based on how the lymph node tissue looks under a microscope. These are called *microscopic subtypes*.

- The **hyaline vascular** type is most common. It tends to be localized, in which case people often have few symptoms and usually have a good outlook, but in rare cases it can be multicentric.
- The **plasma cell** type is more likely to cause symptoms and to be multicentric, but it is sometimes localized.
- The **mixed** subtype shows areas of both hyaline vascular and plasma cell types. It occurs less often.
- The **plasmablastic** type was recognized more recently. Like the plasma cell type, it is usually multicentric, usually causes symptoms, and has a less favorable outlook.

In choosing treatments, doctors believe that the microscopic type is less important than whether the disease is localized or multicentric.

Subtypes of CD based on viral infections

Infection with certain viruses plays a role in at least some cases of CD.

Multicentric CD is more common in people infected with HIV, the virus that causes AIDS. Doctors sometimes group patients with multicentric CD into those who are infected with HIV (HIV positive) and those who are not infected (HIV negative).

In recent years, it's become clear that another virus, known as *human herpesvirus-8* (HHV-8) or *Kaposi sarcoma herpesvirus* (KSHV), is often found in the lymph node cells of people with multicentric CD. In fact, HHV-8 is found in the lymph nodes of nearly all CD patients who are HIV positive. Some doctors have suggested classifying CD based on whether the cells contain HHV-8.

What are the key statistics about Castleman disease?

We don't know how many people are diagnosed with Castleman disease (CD) each year. The National Cancer Institute keeps track of how many people have each type of cancer,

but because CD is not a cancer it is not included. We do know that CD is rare, especially in people who are otherwise healthy.

The localized (unicentric) form of CD is more common than the multicentric form (MCD). MCD is much more likely to occur in people infected with HIV. Over the past few decades, as the number of people with HIV infection has increased, the number of people diagnosed with MCD has also gone up. Modern anti-viral treatments have helped people with HIV live much longer, but these drugs don't seem to lower the chance of getting MCD.

CD can affect children as well as adults. Younger people are more likely to have the localized form. Older adults and those with HIV infection are more likely to have the multicentric form.

For statistics related to survival, see the section "Outlook (prognosis) for people with Castleman disease."

What are the risk factors for Castleman disease?

A risk factor is anything that might change a person's chance of getting a disease. But having a risk factor, or even several, doesn't mean that you will get the disease, and having few or no risk factors doesn't mean you won't get the disease.

Most patients with Castleman disease (CD) don't have any known risk factors.

The only clear risk factor for CD is infection with HIV, the virus that causes AIDS. The multicentric form of Castleman disease is much more common in people with HIV infection, particularly in those who have developed AIDS. This might be because these people tend to have weakened immune systems, which allows for the growth of another virus known as HHV-8 (see "Do we know what causes Castleman disease?"). It's not clear if people who have weakened immune systems for other reasons are also at increased risk.

Do we know what causes Castleman disease?

The main feature of Castleman disease (CD) is an overgrowth of lymphocytes (immune cells) called B cells. The cause of this overgrowth is not known for sure, but it seems to be related to problems with the way a person's immune system is working. Many people with CD have abnormally high blood levels of certain substances made by immune system cells.

For example, in the multicentric form of CD (MCD), the body often makes too much of a protein called interleukin-6 (IL-6). IL-6 normally helps regulate immune function. Too

much IL-6 can cause lymphocytes to grow and divide too quickly. But it's not clear what causes the high levels of IL-6.

One cause seems to be infection with human herpesvirus-8 (HHV-8), also known as Kaposi sarcoma herpesvirus (KSHV) (because it can cause Kaposi sarcoma). HHV-8 is often found in the lymph node cells in people who have MCD, especially those who are HIV positive. HHV-8 can cause infected cells to make a form of IL-6, which could explain how it leads to CD.

Many people are infected with HHV-8, but in people with normal immune systems the virus doesn't seem to cause problems. People infected with HIV, however, often have weakened immune systems, which might allow HHV-8 to grow and cause problems. This could explain why people infected with HIV are more likely get MCD. Still, some people with HIV who develop MCD do not have weakened immune systems, so it's not clear if this is the only reason.

HHV-8 hasn't been found in all cases of MCD. And it's not clear what causes the localized (unicentric) form of CD. Researchers are still looking for the causes of CD in these other cases.

Signs and symptoms of Castleman disease

Castleman disease (CD) can cause a lot of different types of symptoms, and in some people it might not cause any symptoms at all. If symptoms do occur, they are often like those seen with other diseases, such as infections, autoimmune diseases, or even some types of cancer. Because of this, doctors might not suspect CD at first.

Common symptoms of localized CD

The localized form of CD often starts as an enlarged lymph node. If the node is just under the skin, such as in the neck or underarm area, it might be seen or felt as a lump. But if it's in the chest or abdomen (belly), it might not be noticed until it grows large enough to cause other symptoms:

- An enlarged node in the chest might press on the windpipe, which could cause trouble breathing, wheezing, a cough, or a feeling of fullness in the chest.
- An enlarged node in the abdomen can cause trouble eating, pain, or just a feeling of fullness.

In general, most people with localized CD feel well otherwise. In fact, some people have no symptoms at all, and the CD is only found when the doctor does a test for another reason. On the other hand, some people with localized CD can also have some of the other symptoms listed below.

Common symptoms of multicentric CD

People with multicentric CD have more than one area of enlarged lymph nodes. The enlarged nodes can be in the chest or abdomen, but multicentric CD often affects lymph nodes in the groin, the underarm area, and on the sides of the neck, which can often be seen or felt as lumps under the skin.

Multicentric CD can also affect lymphoid tissue of internal organs, causing the liver, spleen, or other organs to enlarge. Enlarged organs might be seen or felt as masses under either side of the rib cage. They can also cause problems eating or a sense of fullness (or even pain) in the abdomen.

In addition, people with either type of CD can have other symptoms (although these symptoms are much more common in people with multicentric CD:

- Fever
- Night sweats (that soak the sheets)
- Weight loss
- Loss of appetite
- Weakness
- Fatigue (tiredness)
- Shortness of breath
- Nausea and vomiting
- Nerve damage that leads to numbness and weakness (neuropathy)
- Leg swelling (edema)
- Skin rashes

Some of these symptoms might come and go over time.

Amyloidosis, a condition where abnormal proteins build up in tissues around the body, can occur in CD. This can lead to kidney damage, heart damage, nerve damage, and intestinal problems, mainly diarrhea. If the CD is treated successfully, the amyloidosis may improve or even go away.

Anemia (having too few red blood cells) is very common in multicentric CD, and can lead to problems such as fatigue and shortness of breath.

CD is rare, and the symptoms above often have other causes. Still, if you have any of these symptoms and they don’t go away within a few weeks (or they get worse), see a doctor so that the cause can be found and treated, if needed.

How is Castleman disease diagnosed?

People with Castleman disease (CD) may see their doctor because of symptoms they are having, or because they just don't feel well and go in for a checkup. Sometimes CD is found in people without symptoms when it's seen on an imaging test being done for another reason.

CD is rare, and its symptoms are often like those caused by other diseases (including infections, autoimmune diseases, and lymphomas), so doctors often suspect it is something else at first. The actual diagnosis of CD is made when doctors remove an affected lymph node and look at it under a microscope. This procedure, known as a *biopsy*, is described below.

Medical history and physical exam

If your symptoms or the results of a test suggest you might have a lymph node problem such as CD, your doctor will want to get a thorough medical history, including the details of any symptoms, possible risk factors, family history, and other medical conditions.

Next, the doctor will examine you, paying special attention to the lymph nodes and other areas of the body that might be involved, including the spleen and liver. Because infections are the most common cause of enlarged lymph nodes, the doctor will look for an infection in the part of the body near the swollen lymph nodes.

If the doctor suspects that CD or another serious problem (such as lymphoma) might be causing the symptoms, he or she might order blood tests, imaging tests, and/or do a biopsy of an affected lymph node (see below).

Blood tests

Blood tests are likely to be done if the doctor suspects CD, some other type of immune system problem, a serious infection, or other conditions. Some of the types of blood tests that can be abnormal in people with CD include:

- Complete blood count (CBC)
- Interleukin-6 (IL-6)
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)

Having abnormal results for these lab tests doesn't prove someone has CD, because other conditions can also cause these problems. But these and other blood tests can help doctors make the right diagnosis.

Imaging tests

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive particles to create pictures of the inside of the body. These tests may be done for a number of reasons, including

- To look for enlarged lymph nodes or organs that might be causing symptoms
- To look for enlarged nodes in other parts of the body
- To help determine if treatment is working

People who might have CD (or another lymph node problem) may have one or more of the following tests.

Computed tomography (CT) scan

The CT scan uses x-rays to make detailed cross-sectional images of your body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help tell if any lymph nodes or organs in your body are larger than normal.

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

Before the scan you might be asked to drink 1 or 2 pints of a contrast agent. This helps outline the intestine so that certain areas aren't mistaken for tumors. You might also need an intravenous (IV) line through which a different kind of contrast dye is injected. This helps better outline structures in your body. The injection can cause some flushing (redness and warm feeling, especially in the face). Some people are allergic and get hives. Rarely, more serious reactions like trouble breathing and low blood pressure can occur. Be sure to tell your doctor if you have any allergies or have ever had a reaction to any contrast material used for x-rays. You can be given medicine to help prevent or treat allergic reactions.

A CT scanner has been described as a large donut, with a narrow table that slides in and out of 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.

CT-guided needle biopsy: CT scans can also be used to guide a hollow biopsy needle precisely into an enlarged lymph node. For this procedure, you remain on the CT scanning table while a doctor moves a biopsy needle through the skin and toward the lymph node. CT scans are repeated until the needle is within the lymph node. A small sample of the node is then removed to be looked at under a microscope. A needle biopsy can't diagnose CD by itself, but it can sometimes help diagnose or exclude other diseases that can cause large lymph nodes.

Magnetic resonance imaging (MRI)

This test is not used as often as CT scans for lymph node problems, but if your doctor is concerned about areas near the spinal cord or brain, MRI is very useful for looking at these areas.

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 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 of radio waves given off by the tissues into a very detailed image of parts of the body. A contrast material might be injected just as with CT scans but is used less often.

MRI scans take longer than CT scans – often up to an hour – and are a little more uncomfortable because you have to lie inside a narrow tube, which is confining and can upset people with a fear of enclosed spaces. 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.

Chest x-ray

This test might be done if you're having breathing problems, to find out if there are enlarged lymph nodes in your chest – usually in the center part of the chest between the lungs called the *mediastinum*.

Ultrasound

Ultrasound uses sound waves and their echoes to create pictures 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 a gel). It gives off sound waves and picks up the echoes as they bounce off the organs. The echoes are converted by a computer into a black and white image that is displayed on a computer screen.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look inside your abdomen for enlarged lymph nodes or organs such as the liver and spleen. It can also show kidneys that have become swollen because the outflow of urine has been blocked by enlarged lymph nodes. (It can't be used to look at organs or lymph nodes in the chest because the ribs block the sound waves.)

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

Positron emission tomography (PET) scan

PET scans are helpful in finding small collections of fast-growing cells that might not be visible on a CT scan. PET is not often used to diagnose CD, but sometimes it can help the doctor determine the cause of enlarged lymph nodes.

For a PET scan, a form of radioactive sugar (known as fluorodeoxyglucose or FDG) is injected into the blood. (The amount of radioactivity used is very low and will pass out of the body over the next day or so.) After about an hour, you are moved onto a table in the PET scanner. You lie on the table for about 30 minutes while a special camera creates a picture showing areas of radioactivity in the body.

Any cancer cells in the body will be growing quickly, so they absorb large amounts of the radioactive sugar. Although CD cells don't take up the sugar as much as cancer cells, they do seem to take it up more than normal cells. The picture from a PET scan is not detailed like a CT or MRI scan, but it can provide helpful information about your whole body.

Often the PET scan is combined with a CT scan, which is more detailed. This helps the doctor determine if abnormal areas seen on the CT scan are CD, cancer, or something else.

Gallium scan

For this test, a solution containing slightly radioactive gallium is injected into a vein. It is attracted to lymph tissue in the body. A few days later a special camera is used detect the radioactivity, showing the location of the gallium. A gallium scan can sometimes find unsuspected sites of CD disease, but it is not always reliable since the gallium might not be taken up by all of the lymph nodes affected by CD.

This test is not used as much now as in the past, as many doctors do a PET scan instead.

Lymph node biopsy

A doctor might suspect you have Castleman disease based on your symptoms or the results of exams or tests, but it can only be diagnosed by removing an enlarged lymph node and examining it under the microscope. This procedure is called a *biopsy*. Different types of biopsies can be used, based on where the lymph node is.

Excisional or incisional biopsy: If the lymph node is near the skin surface, a surgeon can often remove the node using local anesthesia (numbing medicine). The surgeon cuts the skin over the enlarged lymph node, removes the node, and then stitches the cut closed. If the procedure removes the entire lymph node, it is called an *excisional biopsy*. If only part of the node is removed, it is called an *incisional biopsy*.

If the lymph node is in the chest or the abdomen, the surgeon might need to make a large incision to get into either of these places. This type of surgery might require general anesthesia (where you are in a deep sleep), but it might be needed to learn why the lymph node is enlarged.

Sometimes, lymph nodes in the chest can be removed by *mediastinoscopy*. In this procedure, a small cut is made in the front of the neck and a thin, hollow, lighted tube (called a mediastinoscope) is inserted behind the sternum (breast bone) and in front of the

windpipe to look at the area. Special instruments can be passed through this tube to remove all or part of a lymph node.

The same type of procedure can be used to sample lymph nodes in the abdomen. In this case, the test is known as *laparoscopy*. The doctor makes a small cut in the abdomen and inserts a thin, hollow, lighted tube (called a laparoscope) and other instruments to look at the area and remove all or part of a lymph node.

Fine needle aspiration (FNA) or core needle biopsy: Sometimes lymph nodes are biopsied by putting a hollow needle into the node to remove a small amount of tissue. In a fine needle aspiration (FNA) biopsy, the doctor uses a very thin needle to withdraw (aspirate) a small amount of tissue from the enlarged node. For a core needle biopsy, the doctor uses a larger needle to remove a slightly larger piece of tissue.

Doctors have found that diagnosing CD by needle biopsy is sometimes possible, but biopsy methods that remove larger samples of tissue are usually recommended because they are thought to be more accurate.

Lab tests of biopsy samples

All biopsy specimens are looked at under a microscope by a pathologist (a doctor specially trained to diagnose disease), who studies the size and shape of the cells and how they are arranged. Since CD is so rare, the pathologist might ask another pathologist with special training in diagnosing blood and lymph node diseases (called a *hematopathologist*) to look at the biopsy.

Sometimes it’s hard to tell if the lymph node is affected by CD or by lymphoma. In these cases, other tests might be done on the lymph node tissue to help figure this out. Some tests look at the proteins on the surface of the cells, while others look for gene or chromosome changes within the cells. Examples of these lab tests include:

- Immunohistochemistry
- Flow cytometry
- Cytogenetics
- Fluorescent in situ hybridization (FISH)
- Polymerase chain reaction (PCR)

These tests, are described in more detail in our document *Non-Hodgkin Lymphoma*.

How is Castleman disease staged?

When talking about cancer, the *stage* is a description of how far it has spread. The stage helps doctors determine the best treatment and the likely outlook (prognosis) for the patient. Most cancers have a formal staging system that lets doctors sum up the extent of the cancer.

Since Castleman disease (CD) is not a cancer, it doesn't have a formal staging system. Instead, doctors use other important pieces of information to help decide on the best treatment and to give them an idea of how well a patient might do.

The most important factor when deciding on treatment is whether the CD is localized/unicentric or multicentric. Localized/unicentric CD affects only a single lymph node (or lymph node group). The multicentric type affects 2 or more groups of lymph nodes in different parts of the body. It may also affect internal organs like the spleen or liver. Tests are done to see what lymph nodes and organs are affected to learn which type of CD a patient has. These tests often include some of the imaging tests mentioned in the section "How is Castleman disease diagnosed?" such as a chest x-ray and either a CT scan or MRI of the chest and abdomen.

Another factor is the microscopic subtype of the CD, which is a description of the patterns of cells seen under the microscope in the biopsy sample. These subtypes are described in the section "What is Castleman disease?"

A third important factor is whether or not the patient is infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. Just about all people infected with HIV who develop CD will have the multicentric form of the disease.

Outlook (prognosis) for people with Castleman disease

Survival rates are often used by doctors as a standard way of discussing a person's outlook (prognosis). Some people may want to know statistics on the outlook for those in similar situations, while others may not find the numbers helpful, or may even not want to know them. If you don't want to know about the outlook for people with different types of Castleman disease (CD), stop reading here and skip to the next section.

It's hard to get accurate numbers on the outlook for people with CD because it is rare. Most statistics on the disease come from small numbers of patients who were treated at a single center or hospital. These numbers might not accurately reflect the outcomes for all people with CD.

The numbers below come from a study of nearly 200 people treated for CD in many different centers. The study divided people into groups based on whether the CD was unicentric or multicentric, its microscopic subtype, and whether the patient was infected with HIV (HIV+) or not infected (HIV-).

The 3-year disease-free survival (DFS) rate refers to the percentage of patients who were still alive and had no signs of CD at least 3 years after it was diagnosed. Of course, many people went much longer than 3 years without any signs of CD (and many were likely cured).

Type of Castleman Disease	3-Year Disease-Free Survival
Unicentric, hyaline vascular, HIV-	93%
Unicentric, plasma cell or mixed, HIV-, OR Multicentric, hyaline vascular, HIV-	79%
Multicentric, plasma cell, HIV-	46%
HIV+ (multicentric)	28%

Even when taking the factors above into account, disease-free survival rates are at best rough estimates. If you have CD, your doctor can tell you how well these numbers might apply to you, as he or she knows your situation best.

How is Castleman disease 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 health 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.

General treatment information

Once you have been diagnosed with Castleman disease (CD), your health care team will discuss treatment options with you. Several different types of treatment can be used for CD:

- Surgery
- Radiation therapy
- Corticosteroid drugs
- Chemotherapy
- Immunotherapy

- Anti-viral drugs

Your treatment options will depend on the whether the CD is localized (unicentric) or multicentric, as well as other factors. Because CD is rare, it has been hard to do studies to learn the best ways to treat it. Of course, no two patients are exactly alike, so treatment is tailored to each person's situation.

Based on your treatment options, you can have different types of doctors on your treatment team. These doctors might include:

- A surgeon
- A hematologist: a doctor who treats disorders of the blood and lymph system, including CD
- A medical oncologist: a doctor who treats cancer and similar diseases with medicines
- A radiation oncologist: a doctor who treats cancer and similar diseases with radiation therapy

Many other specialists might be part of your treatment team as well, including physician assistants, nurse practitioners, nurses, nutrition specialists, social workers, and other health professionals. See *Health Professionals Associated With Cancer Care* for more on this.

It's important to discuss all of your treatment options, including the goals of treatment and possible side effects, with your doctors to help make the decision that best fits your needs. In choosing a treatment plan, consider your health and the type of CD. Be sure that you understand all the risks and side effects of the various treatments before making a decision. Ask your health care team questions. You can find some good questions to ask in the section "What should you ask your doctor about Castleman disease?"

CD is a rare disease, so not many doctors have much experience treating it. If time allows, it's often a good idea to seek a second opinion. Getting a second opinion can give you more information and help you feel confident about the treatment plan that you choose. Your doctor should be willing to help you find another doctor who can give you a second opinion.

The next few sections describe the types of treatment used for Castleman disease. This is followed by a discussion of the typical treatment options based on whether the CD is localized (unicentric) or multicentric, as well as other factors when these are important.

Surgery for Castleman disease

Surgery is often used to obtain a tissue sample to diagnose Castleman disease (CD). A lymph node biopsy (described in "How is Castleman disease diagnosed?") is usually a minor procedure, and patients can often go home afterwards.

Surgery also works well to treat localized (unicentric) CD. The type of surgery depends on where the disease is located.

If the affected lymph node or nodes are in a place that is easy to get to, such as in the armpit, then surgery is usually straightforward. In many cases the person may even be able to go home the same day after the surgery.

When the enlarged lymph nodes are in a place that is hard to get to, like deep in the chest or abdomen, surgery is more complex and might require a stay in the hospital for a few days after the operation.

Surgery is also sometimes used in multicentric disease, although in this case it's used to help treat symptoms rather than to try to cure the disease. For example, the spleen can be removed if it has grown large and is causing symptoms.

Potential side effects of surgery depend on several factors, including the extent of the operation and a person's health before surgery. Most people will have at least some pain after the operation, but it usually can be controlled with medicines if needed. Other problems can include reactions to anesthesia, damage to nearby organs during the operation, bleeding, blood clots in the legs, and skin infections at the incision sites.

Even though Castleman disease is not a cancer, surgery is often used in much the same way as it is for cancer. You can read more in *Understanding Cancer Surgery: A Guide for Patients and Families*.

Radiation therapy for Castleman disease

Radiation therapy uses high-energy radiation to kill cells. It is sometimes used to treat localized Castleman disease (CD), especially if the affected lymph nodes can't be removed completely with surgery. Radiation can also be used as part of the treatment for multicentric CD.

Radiation focused from a source outside the body is called *external beam radiation*. The treatment is much like getting an x-ray, but the radiation is more intense. Before the treatments start, the radiation team takes careful measurements to determine the correct angles for aiming the radiation beams and the proper dose. Each treatment lasts only a few minutes, although the setup time – getting you into place for treatment – usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks.

Common side effects of radiation can include skin problems (like a sunburn) in areas that get radiation and fatigue. Radiation to the abdomen can cause nausea, diarrhea, and loss of appetite. These side effects tend to improve a short while after the radiation is stopped. Radiation to the chest area can damage the heart and lungs. This might eventually lead to problems such as shortness of breath or an increased risk of heart attacks. Radiation can also make the side effects of chemotherapy worse if they both are given at the same time.

Even though Castleman disease is not a cancer, radiation is often used in the same way as it is when people have cancer. To learn more, see the "Radiation Therapy" section of our website, or our document *Understanding Radiation Therapy: A Guide for Patients and Families*.

Corticosteroids for Castleman disease

Corticosteroids are a group of drugs related to hormones made in the body by the adrenal glands. These drugs weaken the immune system, so they are useful in treating people with certain immune system diseases and cancers that develop from immune system cells, such as lymphomas.

In some patients with multicentric Castleman disease (CD), these drugs can helpful, either alone or along with chemotherapy.

Corticosteroids are often taken as pills, but they can also be given as an injection into a vein. Prednisone is the corticosteroid pill most often used to treat CD.

Side effects of corticosteroids (especially long-term use) can include increased blood sugar (which can lead to diabetes), mood changes, increased risk of infections, weakened bones, fatigue, muscle weakness, weight gain, fluid retention, and high blood pressure. Most of these side effects improve after the drug is stopped.

Chemotherapy for Castleman disease

Chemotherapy (chemo) is the use of anti-cancer drugs that are injected into a vein or a muscle or are taken by mouth. These drugs enter the bloodstream and reach all areas of the body, making this treatment very useful for multicentric Castleman disease (CD). Chemo may be used alone, in combination with corticosteroids or other drugs, or combined with radiation therapy (called *chemoradiation*).

Many chemo drugs can be used to treat patients with multicentric CD. The drugs used most often include:

- Carmustine
- Cladribine
- Chlorambucil
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Melphalan
- Vinblastine
- Vincristine

Often several drugs are combined. Because CD is similar to lymphomas in many ways, doctors often use chemo combinations like those used for lymphoma. But because CD is

so rare, there is not a lot of information on which chemo treatment is best or even how well it works.

Doctors give chemo in cycles, in which a period of treatment is followed by a rest period to give the body time to recover. Each chemo cycle generally lasts for several weeks. Most chemo treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department) but some might require a hospital stay. Sometimes a patient takes one drug combination for several cycles and then later is switched to a different one.

Possible side effects

Chemo drugs attack cells that are dividing quickly, which is why they work against cancer and diseases like CD. But other cells in the body, such as those in the bone marrow (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells can also be affected by chemo, which can lead to certain side effects.

The side effects of chemo depend on the type and dose of drugs given and the length of time they are taken. These side effects can include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea
- Increased risk of infections (due to a shortage of white blood cells)
- Easy bruising and bleeding (due to a shortage of blood platelets)
- Fatigue and weakness (due to a shortage of red blood cells)

Most side effects improve once treatment is stopped, but some can last a long time or even be permanent. If your doctor plans treatment with chemo, be sure to discuss the drugs that will be used and the possible side effects.

If you get chemo, tell your doctor or nurse about any side effects as soon as you notice them. Your cancer care team can help you deal with them.. For example, drugs can be given before or along with chemo to help prevent or reduce nausea and vomiting.

Certain chemo drugs can have other, more specific side effects. For example, some can damage organs such as the kidneys or heart. Some of the drugs used to treat CD can cause nerve damage (known as *peripheral neuropathy*), leading to problems such as numbness and tingling in the hands and feet.

If you have serious side effects, the chemo might need to be reduced or stopped, at least for a short time. Your doctor will carefully monitor and adjust your drug doses because some side effects might be permanent.

Even though Castleman disease is not a cancer, chemo is often used in much the same way as it is for cancer. To learn more, see the “Chemotherapy” section of our website, or our document *A Guide to Chemotherapy*.

Immunotherapy for Castleman disease

Immunotherapy is treatment that either boosts the patient’s own immune system or uses man-made versions of the normal parts of the immune system.

Monoclonal antibodies

Antibodies are proteins made by the body’s immune system to help fight infections. Man-made versions, called *monoclonal antibodies*, can be designed to attack a specific target, such as a substance on the surface of lymphocytes, the cells in which Castleman disease (CD) starts.

Siltuximab (Sylvant™): This monoclonal antibody is used to treat some patients with multicentric CD. These patients often have high levels of a protein called IL-6. Siltuximab binds to IL-6, which keeps the protein from acting on lymphocytes. This drug doesn’t seem to bind to IL-6 that is made from viruses, so it isn’t meant for patients who are infected with either HIV or HHV-8. (IL-6, HIV, and HHV-8 were discussed in the section “Do we know what causes Castleman disease?”)

This drug is given as an infusion into a vein (IV), usually every 3 weeks.

Side effects tend to be mild and can include rash, itching, swelling, and weight gain. Some patients can also have side effects during the infusion, such as flushing (skin redness with a feeling of warmth), chest pain, back pain, nausea, and rapid heartbeat.

Rituximab (Rituxan®): This monoclonal antibody is widely used for lymphoma. It can also be helpful in treating CD. Rituximab attaches to a protein called CD20 that is found on the surface of some lymphocytes. This attachment causes the cell to die.

Patients get rituximab through infusion into a vein (IV) at the doctor’s office or clinic. It is often given along with chemotherapy.

Side effects of rituximab are most common during the infusion, and can include chills, fever, nausea, rashes, fatigue, and headaches. Rarely, more severe side effects occur during the infusion, such as trouble breathing and low blood pressure. Unlike regular chemotherapy, rituximab does not cause low blood counts or hair loss.

This drug can also increase a person’s risk of certain infections. In people who have ever been infected with the hepatitis B virus, this drug can sometimes cause the infection to become active again. Your doctor may check your blood for signs of a prior hepatitis infection before starting this drug to see if it is safe.

Other antibodies: Newer antibodies that attack other targets are also being studied for use against CD. These are discussed in the section “What’s new in research and treatment of Castleman disease?”

Immunomodulating drugs (IMiDs)

Drugs such as thalidomide (Thalomid®) and lenalidomide (Revlimid®) are used to treat certain cancers of immune cells such as multiple myeloma and some types of lymphoma, but they have also helped some patients with CD.

These drugs are thought to work by affecting parts of a person’s immune system. It’s not exactly clear how they do this, but it seems to be at least in part by working against interleukin-6 (IL-6).

The drugs can cause side effects such as drowsiness, fatigue, constipation, low blood cell counts, and neuropathy (painful nerve damage). There is also an increased risk of serious blood clots (that start in the leg and can travel to the lungs). These tend to be more likely with thalidomide.

Because of concerns these drugs can cause severe birth defects if taken during pregnancy, they can only be obtained through special programs run by the drug company that makes them.

Interferon-alfa

Interferon-alfa is a hormone-like protein made by white blood cells in the body to help the immune system fight infections. Some patients with CD have improved with man-made interferon treatment.

Interferon is given by an injection, either daily or several times a week. This may be into a vein (IV), under the skin (SubQ), or into a muscle (IM). It may be given in a doctor’s office, or you or a family member can be taught how to give the medicine under the skin.

Side effects of this treatment can include fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. Because of these side effects, interferon is not used very often. It may be given to some patients in addition to chemotherapy.

Anti-viral drugs for Castleman disease

Multicentric Castleman disease (CD) is sometimes associated with the virus HHV-8. Doctors have had success in treating some patients with multicentric CD with drugs that kill this virus, such as ganciclovir, valganciclovir, and foscarnet.

Many patients with HIV infection are treated with anti-retroviral therapy to keep the HIV in check. But the effect of therapy for HIV on CD is not clear.

Clinical trials for Castleman disease

You may have had to make a lot of decisions since you've been told you have Castleman disease (CD). One of the most important decisions you will make is choosing which treatment is best for you. You may have heard about clinical trials being done for CD. Or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to learn more about promising new treatments or procedures.

Clinical trials are one way to get state-of-the art treatment. Sometimes they may be the only way to get some newer treatments. They are also the best way for doctors to learn better methods to treat CD. Still, they are not right for everyone.

If you would like to learn more about clinical trials that might be right for you, start by asking your doctor if your clinic or hospital conducts clinical trials. You can also get a list of current clinical trials by visiting the US National Institutes of Health (NIH) clinical trials website at www.clinicaltrials.gov.

You must meet certain requirements to take part in any clinical trial. If you do qualify for a clinical trial, it is up to you whether or not to enter (enroll in) it.

You can get a lot more information on clinical trials in our document *Clinical Trials: What You Need to Know*.

Complementary and alternative therapies for Castleman disease

When you have Castleman disease (CD) you are likely to hear about ways to treat your disease or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to social media groups and websites may offer ideas for what might help you. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

What exactly are complementary and alternative therapies?

Not everyone uses these terms the same way, and they are used to refer to many different methods, so it can be confusing. We use *complementary* to refer to treatments that are used *along with* your regular medical care. *Alternative* treatments are used *instead of* a doctor's medical treatment.

Complementary methods: Most complementary treatment methods are not offered as cures for CD. Mainly, they are used to help you feel better. Some methods that are used along with regular treatment are meditation to reduce stress, acupuncture to help relieve pain, or peppermint tea to relieve nausea. Some complementary methods are known to help, while others have not been tested. Some have been proven not to be helpful, and a few have even been found harmful.

Alternative treatments: Alternative treatments may be offered as CD cures. These treatments have not been proven safe and effective in clinical trials. Some of these methods may pose danger, or have life-threatening side effects. But the biggest danger in most cases is that you may lose the chance to be helped by standard medical treatment. Delays or interruptions in your medical treatments may give your disease more time to grow and make it less likely that treatment will help.

Finding out more

It is easy to see why people with CD may think about alternative methods. You want to do all you can to fight your disease, and the idea of a treatment with few or no side effects sounds great. Sometimes medical treatments like chemotherapy can be hard to take, or they may no longer be working. But the truth is that most of these alternative methods have not been tested and proven to work in treating CD.

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

- Look for “red flags” that suggest fraud. Does the method promise to cure all or most diseases? Will you be evaluated by a qualified clinician? Are you told not to have regular medical treatments? Is the treatment a “secret” that requires you to visit certain providers or travel to another country?
- Talk to your doctor or nurse about any method you are thinking about using.
- Contact us at 1-800-227-2345 or see the “Complementary and Alternative Medicine” section of our website to learn more about complementary and alternative methods in general and to find out about the specific methods you are looking at..

The choice is yours

Decisions about how to treat or manage your disease are always yours to make. If you want to use a non-standard treatment, learn all you can about the method and talk to your doctor about it. With good information and the support of your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treatment of localized (unicentric) Castleman disease

Surgery is the recommended treatment for people with localized Castleman disease (CD) whenever possible. Removing the abnormal lymph node(s) usually cures the disease. Symptoms such as fever and fatigue that are caused by the CD go away when the lymph node is removed. Relapses are rare.

Sometimes if the diseased area is too large to be removed by surgery, medicines such as corticosteroids or rituximab might be given first. This can shrink the tumor and make it easier to remove.

Radiation can also be used to treat localized CD, either in people who can't have surgery for some reason or if not all of the disease can be removed with surgery. But it's not used as often as surgery as the main treatment.

Some patients with localized CD develop secondary amyloidosis, a condition in which abnormal proteins build up in the kidneys, skin, and some other organs. This protein build-up stops once the lymph node affected by CD is removed.

The outlook for localized CD is very good if the affected lymph node(s) can be removed with surgery (or treated with radiation). But sometimes not all of the disease can be removed or treated safely. This doesn't necessarily mean it will continue to grow and get worse. Even partial removal may help, and the disease may not grow back.

Treatment of multicentric Castleman disease

Multicentric Castleman disease (MCD) is usually much harder to treat than localized CD. There is no standard therapy for MCD, and no single treatment works for all patients. Several types of treatment have been shown to help some patients. But because MCD is rare, it has been hard for doctors to compare different treatments against each other in clinical trials.

Surgery is used to biopsy an affected lymph node to make the diagnosis, but MCD is too widespread to remove it all with surgery or treat it effectively with radiation. Still, some people are helped by these treatments. For example, surgery is sometimes used to remove an enlarged spleen that is causing symptoms, or radiation can be used to shrink tumors in a specific area that are causing problems.

More often, doctors use treatments that can reach all parts of the body, such as corticosteroids, chemotherapy, or immunotherapy, when treating MCD. Doctors usually try one or a combination of these treatments to try to put the disease into remission. Anti-viral drugs including anti-HIV treatment may also help.

In some patients the disease shrinks or even goes away completely with treatment, at least for a time. In others, the benefit does not last long and symptoms come back once treatment is stopped. Some patients may not be helped by these drugs at all.

In people whose MCD is no longer responding to other treatments, some doctors might recommend high-dose chemotherapy followed by a stem cell transplant. There are a few reported cases of this being successful. This is a complex, serious, and often expensive treatment, so it's important to understand what it might entail if you are considering this option. For more on this treatment, see our document *Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants).*

The long-term outlook (prognosis) for people with MCD is often not as good as for people with localized CD. Treatment can often help for a time, but the disease tends to come back within a couple of years. A major concern is that people with MCD are at risk of dying from other causes, like serious infections or progression of the MCD to a fast-growing form of lymphoma that is hard to treat. (For more information about lymphoma, see our document *Non-Hodgkin Lymphoma*.)

The outlook for MCD tends to be worse if the person also has HIV/AIDS. Even if the HIV infection is under control with drug treatment, the MCD is not likely to go away. The treatment and outlook of MCD can also be complicated by the presence of Kaposi sarcoma and other AIDS-related conditions. These conditions may be less of a problem if the patient is on anti-HIV treatment.

Because MCD can be hard to treat, taking part in a clinical trial of newer treatments can be a good option for some people. (See “What’s new in research and treatment of Castleman disease?” for a description of some newer treatments.)

What should you ask your doctor about Castleman disease?

As you cope with Castleman disease (CD) and its treatment, we encourage you to have honest, open discussions with your doctors. Feel free to ask any question that’s on your mind, no matter how small it might seem. Here are some questions you might want to ask. Be sure to add your own questions as you think of them. Nurses, social workers, and other members of the treatment team might also be able to answer many of your questions.

- Is my CD localized or multicentric?
- Has my biopsy been reviewed by a pathologist who is an expert on CD?
- Do I also have HIV infection and AIDS? If so, how does it influence my prognosis (outlook) and treatment of CD?
- Do I need other tests before we can decide on treatment?
- Are there other doctors I need to see?
- How much experience do you have treating CD?
- Should I get a second opinion before starting treatment? Can you suggest a doctor or treatment center?
- What treatment choices do I have? Do we need to start treatment right away?
- Which treatment do you recommend, and why?
- What are the side effects of the treatments that you recommend?
- What can I do to help reduce the side effects I may have from the treatment?
- 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 my outlook for survival?
- What are the chances of the CD coming back with these treatment plans?
- What would we do if the treatment doesn't work or if the CD comes back?
- What type of follow-up will I need after treatment?
- Am I eligible for clinical trials of any new treatments?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so that you can plan your work or activity schedule.

What happens after treatment for Castleman disease?

For many people with Castleman disease (CD), treatment can remove or destroy the disease. Completing treatment can be both stressful and exciting. You may be relieved to finish treatment, but find it hard not to worry about the CD coming back. (When the disease comes back after treatment, it is called *recurrence*.) This is a very common concern in people with serious diseases such as CD.

For some people, the CD may never go away completely. These people may get regular treatments with chemotherapy, corticosteroids, or other therapies to help keep the CD in check for as long as possible. Learning to live with CD as a more of a chronic disease can be difficult and very stressful. It has its own type of uncertainty.

Follow-up care

If you have completed treatment, frequent follow-up exams are very important for several years after the treatment is finished. The doctors will continue to watch you for signs of recurrent disease, as well as for short-term and long-term side effects of treatment. It's important to report any new symptoms to the doctor right away, so that relapse or side effects can be treated.

Checkups usually include careful physical exams, imaging tests such as CT scans when needed, and lab tests to look for signs of CD or treatment side effects. Almost any type of treatment can have side effects. Some can last for a few weeks to months, but others can last the rest of your life.

CD can come back in some people. Multicentric CD may come back as soon as the first year after treatment. If the CD does recur at some point, further treatment will depend on what treatments you've had before, how well they worked, how long it's been since treatment, and your overall health.

Some people with multicentric CD (especially those who are HIV-positive) might develop non-Hodgkin lymphoma or Kaposi sarcoma at some point. These cancers can be hard to treat, so it helps to diagnose and treat them as early as possible.

What's new in research and treatment of Castleman disease?

Research into the causes and treatment of Castleman disease (CD) is being done in many medical centers throughout the world. Unfortunately, research into this disease is slowed by the fact that CD is rare.

Causes

Doctors have learned a great deal about some of the possible causes of CD in recent years. For example, many people with multicentric CD (MCD) have been found to have evidence of infection with human herpesvirus-8 (HHV-8) in their lymph nodes. This type of information might help researchers come up with new ways of treating this disease.

But there's a lot we still don't know about the exact causes of CD. This is now under study.

Treatment

Researchers have begun to study several promising new drugs for use against CD in recent years.

Many patients with MCD have too much of a protein called interleukin-6 (IL-6) in their blood. Drugs that target IL-6 have shown promise against MCD. One of these drugs, siltuximab, is a monoclonal antibody that binds to IL-6, which stops it from reaching lymphocytes. This drug is now approved for use in people with MCD who are not infected with HIV or HHV-8 (see "Immunotherapy for Castleman disease").

Another monoclonal antibody, tocilizumab (Actemra®), blocks the action of IL-6 by binding to its receptor on lymphocytes. This drug is being studied for use against MCD. It is already approved to treat rheumatoid arthritis in the United States, and some doctors use it to treat MCD as well.

It is unclear how helpful these drugs will be in MCD patients who are HIV-positive, since few HIV-positive patients have been in the studies so far. Still, these drugs offer hope for the future treatment of MCD.

Other drugs being studied for treatment of CD include:

- Sirolimus, cyclosporine, and mycofenolate mofetil: These drugs suppress the immune system, so they are often used in autoimmune diseases or to help prevent the rejection of organ transplants, but they may also be helpful in CD.

- Suramin: This drug is thought to work by stopping IL-6 from attaching to and affecting lymphocytes.
- Bortezomib (Velcade): This drug is used mainly to treat multiple myeloma, but some reports also suggest it might help some people with CD.
- CX-4945: This drug blocks CK2, a protein that helps some cells grow and divide. It is still in the earliest phases of testing.

Additional resources for Castleman disease

More information from your American Cancer Society

We have some related information that may also be helpful to you. These materials may be viewed on our website or ordered from our toll-free number, 1-800- 227-2345.

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

A Guide to Chemotherapy (also available in Spanish)

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

Cancer Immunotherapy

Clinical Trials: What You Need to Know

HIV, AIDS, and Cancer

Non-Hodgkin Lymphoma

Your American Cancer Society also has books that you might find helpful. Call us at 1-800-227-2345 or visit our bookstore online at cancer.org/bookstore to find out about costs or to place an order.

National organizations and websites*

Along with the American Cancer Society, other sources of information and support include:*

National Organization for Rare Disorders (NORD)
Phone number: 1-203-744-0100
Toll-free number: 1-800-999-6673 (voicemail only)
Website: www.rarediseases.org

> Offers a rare disease database, including information on Castleman disease, and some patient assistance programs for specific illnesses. They also offer referrals to other organizations, resources, and support groups for rare diseases.

International Castleman's Disease Organization
Website: www.castlemans.org

Offers information and resources for people with Castleman Disease

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

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at 1-800-227-2345 or visit www.cancer.org.

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