### **Erdheim-Chester disease (ECD)**

Erdheim-Chester disease (ECD) is a rare blood disorder that can affect various organs in your body. ECD belongs to a group of rare disorders called histiocytosis. With histiocytosis, there’s an abnormal increase in certain immune cells called histiocytes. Histiocytes are an important part of your immune system.

They’re normally found in many parts of your body, including your bone marrow, bloodstream, skin, lungs, spleen and liver.

With ECD, histiocytes grow out of control. The excess histiocytes may travel to different parts of your body where they’re not usually found and cause tumors. The histiocytes invade tissue and cause damage.

ECD is rare, with only about 800 reported cases worldwide since the condition was discovered in 1930. It’s likely underdiagnosed. Currently, there aren’t general reporting guidelines that nations use to keep track of diagnoses.

Erdheim-Chester disease is most common in middle-aged adults, but children have been diagnosed in rare instances. The average age of diagnosis in the U.S. is 46. ECD is more common in men, who account for 70% to 75% of diagnoses.

## **Symptoms and Causes**

ECD affects people differently. Symptoms vary depending on which parts of your body have excess histiocytes and which body systems are affected. In some instances, Erdheim-Chester disease is asymptomatic, which means it doesn’t cause symptoms. In that case, your healthcare provider may see evidence of ECD during imaging or lab tests.

#### **Bones**

ECD can cause abnormal hardening in your bones (osteosclerosis), sometimes, resulting in bone pain. Bone hardening, often affecting both legs, usually shows up in imaging to diagnose ECD. Bone pain in both legs is the most common symptom of ECD.

#### **Kidneys**

ECD can damage your kidneys and tissue in the body cavity that contains your kidneys and other abdominal organs (retroperitoneum). The invading histiocytes may cause:

* Kidney swelling.
* Kidney atrophy.
* Renal failure (kidney failure).

#### **Endocrine system**

Invading histiocytes can damage glands that release hormones that help regulate important processes in your body. Depending on which gland is damaged, you may experience symptoms of:

* Hypopituitarism (too little of one or more hormones your pituitary gland makes).
* Hypothyroidism (too little of one or more hormones your thyroid gland makes).
* Hypogonadism (too few sex hormones, like testosterone or estrogen).
* Adrenal insufficiency (too few hormones made by your adrenal gland).

Damage to your pituitary gland can cause symptoms of diabetes insipidus, like frequent peeing and thirst. Up to half of the people with ECD are also diagnosed with diabetes insipidus.

#### **Nervous system**

Histiocytes can damage tissue in your brain and nervous system. Symptoms may include:

* Problems with coordination and balance (ataxia).
* Slurred speech because of poor control over your speaking muscles (dysarthria).
* Trouble thinking, concentrating or remembering.
* Headaches.

#### **Eyes**

ECD may affect one or both eyes. Symptoms include:

* Soft, yellowy growths on your eyelids (xanthelasma).
* Bulging eyeballs (proptosis).
* Eye pain.
* Vision loss.

#### **Respiratory system**

Excess histiocytes affecting your lungs often appear on imaging but don’t cause symptoms. If you do experience symptoms, they may include:

* Cough.
* Shortness of breath (dyspnea).

Left untreated, ECD can cause serious, long-term lung scarring (pulmonary fibrosis).

#### **Cardiovascular system**

Your healthcare provider may see evidence of excess histiocytes affecting your heart and blood vessels on imaging. The damage may be life-threatening without treatment. ECD may cause:

* Fluid build-up and swelling in the sac surrounding your heart (pericardial effusion).
* High blood pressure that results from restricted blood flow to your kidneys (renal hypertension).
* Heart failure.

#### **Skin**

The most common sign of ECD on your skin is yellowish growths on your eyelids. Yellowish-brown growths may also appear on your:

* Face.
* Neck.
* Torso.
* Groin.

Excess histiocytes can also collect in your spleen, liver and bone marrow, causing tissue damage.

### **What causes Erdheim-Chester disease?**

With ECD, histiocytes multiply out of control and spread, damaging healthy tissue and organs. Scientists aren’t sure what causes the out-of-control cell growth in all instances, but they’ve recently discovered gene mutations (changes) that likely play a role.

More than half of people with Erdheim-Chester disease have a mutation in the *BRAF* gene that promotes uncontrolled histiocyte growth. Although *BRAF* is the most common site for gene mutations with ECD, scientists have also discovered other gene mutations associated with ECD.

These discoveries have allowed scientists to develop treatments that target mutations and prevent abnormal histiocyte growth.

## **Diagnosis and Tests**

ECD is so rare and presents so differently across individuals that healthcare providers may not immediately suspect it. Receiving a diagnosis may take time. You may work with several healthcare providers before receiving a diagnosis.

Your healthcare providers will consider your symptoms alongside the results of several other procedures and tests before diagnosing you with ECD. Diagnosis involves:

* Imaging procedures: Various imaging studies allow your provider to see where excess histiocytes are invading tissue throughout your body. X-rays and bone scans can show if your bones are affected. A PET scan can show bone damage and soft tissue damage. A CT scan and MRI can show soft tissues that may be affected, including your brain and organs in your chest and abdomen.
* Lab tests: Lab tests can show issues with organ functioning that may be related to ECD. Your healthcare provider may also check for signs of inflammation, irregular blood cell counts or atypical hormone levels.
* Biopsy: During a biopsy, a provider removes a tissue sample and views it beneath a microscope to check cells for signs of ECD. They’ll test the cells for mutations (like *BRAF*) associated with ECD. Learning these cell characteristics can help your provider determine which treatments will work best.

## **Management and Treatment**

If you don’t have symptoms and ECD isn’t negatively impacting your body, your healthcare provider may choose to monitor your condition. Still, most people with ECD need treatment. While there isn’t a cure, several treatments can help manage Erdheim-Chester disease. Treatments include:

* Targeted therapy: Targeted therapy includes drugs targeting the gene mutations that cause histiocytes to multiply out of control. These treatments interfere with the process that causes histiocytes to behave abnormally. Vemurafenib is a U.S. Food and Drug (FDA)-approved drug used to treat ECD involving *BRAF* gene mutations. Cobimetinib is an FDA-approved drug for treating ECD involving *MEK* mutations. Your healthcare provider may recommend Vemurafenib or cobimetinib, other targeted therapy drugs or a combination of drugs depending on the types of cell mutations they discover during testing.
* Immunotherapy: Immunotherapy drugs help your immune system identify and fight cancer cells more effectively. Interferon-alpha is a common immunotherapy drug used to treat ECD.
* Chemotherapy: Chemotherapy uses drugs to destroy cancer cells and prevent tumor growth throughout your body. The most common chemotherapy drug used to treat ECD is cladribine. Still, your provider may recommend other chemotherapy drugs or drug combinations.

Your healthcare provider may recommend additional treatments to help with symptom relief. These treatments can’t prevent histiocytes from invading tissue, but they can help you feel better.

* Surgery: You may need surgery to address tissue damage resulting from ECD. For example, inflammation and damaged tissue can block the tubes that carry urine (pee) from your bladder (ureters). You may need surgery to correct this issue or others.
* Radiation therapy: Your provider may recommend radiation therapy to destroy cancer cells that are causing unpleasant symptoms in a specific part of your body.
* Corticosteroids: Corticosteroids can ease inflammation associated with invading histiocytes.

You may also be eligible for a clinical trial. A clinical trial is a study that tests new treatments and new treatment combinations for safety and effectiveness. Ask your provider if you should participate in a clinical trial for Erdheim-Chester disease.

## **Outlook / Prognosis**

Your prognosis depends on where the histiocytes have caused damage in your body and your response to treatment. Still, recent advancements in treatments, such as targeted therapy, have improved the outcomes associated with ECD.

In 1996, the five-year survival rate for ECD was 43%. According to a recent study, the survival rate has increased to 83%.

Talk to your provider about your prognosis based on your condition and response to treatment.

## **Prevention**

Erdheim-Chester disease isn’t preventable, but it’s often manageable with treatment.

### **When should I see my healthcare provider?**

ECD requires ongoing treatment and monitoring. Your provider will advise you on how often you’ll need follow-up visits, including imaging procedures and lab work.

Many of the treatments used for ECD may cause unpleasant side effects. Working with a palliative care team in addition to your ECD care team can help you manage these treatment side effects as you navigate your ECD diagnosis.

**Differential diagnosis (DDX) for Erdheim-Chester disease (ECD)**

Langerhans Cell Histiocytosis (LCH)

* Neurosarcoidosis
* Hypophysitis (including lymphocytic, granulomatous, xanthomatous, xanthogranulomatous, necrotising types)
* Retroperitoneal fibrosis (Ormond’s disease)
* IgG4-related disease
* Rosai-Dorfman disease
* Takayasu arteritis
* Wegener’s granulomatosis (Granulomatosis with polyangiitis)
* Chronic recurrent multifocal osteomyelitis
* Malignancies (e.g., lymphoma)
* Mycobacterial infections
* Metabolic disorders (e.g., Gaucher disease)
* Rheumatic diseases (due to overlapping systemic inflammatory symptoms)
* Other histiocytoses

**EPIDEMIOLOGY**

Incidence: Approximately 0.35 cases per 1,000,000 adult residents per year in combined studies from Italy and France (2018–2020) . In the United States, incidence estimates are around 0.9 cases per 10 million population .

Age at Diagnosis: Typically develops in adults, with a peak incidence between 46 and 60 years of age . Median age at diagnosis ranges from early 50s to early 60s in different cohorts .

Sex Ratio: Strong male predominance with a male-to-female ratio of approximately 3:1 .

Geographic Clustering: Cases cluster in specific regions such as southern Italy and central France, and disease frequency inversely correlates with the Human Development Index .

Number of Reported Cases: Worldwide, over 1,500 cases have been reported since its first description in 1930 .

Pediatric Cases: Extremely rare, with fewer than 15 pediatric cases reported .

Organ Involvement: Most patients have multiorgan involvement, commonly bones (80–90%), perirenal tissue, central nervous system, heart, large vessels, skin, lungs, and others .

Survival: Median survival from onset is around 10 years, with improved survival in recent decades due to targeted therapies

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### **Thalassemia**

Thalassemia (thal-uh-SEE-me-uh) is an inherited blood disorder. It affects your body’s ability to produce normal hemoglobin. Hemoglobin is a protein in red blood cells. It allows your red blood cells to transport oxygen throughout your body, nourishing your body’s other cells.

If you have thalassemia, your body produces fewer healthy hemoglobin proteins, and your bone marrow produces fewer healthy red blood cells. The condition of having fewer red blood cells is called anemia. As red blood cells serve the vital role of delivering oxygen to tissues in your body, not having enough healthy red blood cells can deprive your body’s cells of the oxygen they need to make energy and thrive.

### **How does thalassemia affect my body?**

Thalassemia can cause mild or severe anemia and other complications over time (such as iron overload). Symptoms of anemia include:

* Fatigue.
* Trouble breathing.
* Feeling cold.
* Dizziness.
* Pale skin.

### **Who is at risk for thalassemia?**

The gene mutations that cause thalassemia arose in humanity as partial protections against malaria. So, thalassemia affects people who have ancestral links to parts of the world where malaria is prevalent, such as Africa, Southern Europe and West, South and East Asia. Thalassemia is inherited, which means the condition is passed from a biological parent to their child.

## **Symptoms and Causes**

Hemoglobin consists of four protein chains, two alpha globin chains and two beta globin chains. Each chain — both alpha and beta — contains genetic information, or genes, passed down from your parents. Think of these genes as the “code” or programming that controls each chain and (as a result) your hemoglobin. If any of these genes are defective or missing, you’ll have thalassemia.

* Alpha globin protein chains consist of four genes, two from each parent.
* Beta globin protein chains consist of two genes, one from each parent.

The thalassemia you have depends on whether your alpha or beta chain contains the genetic defect. The extent of the defect will determine how severe your condition is.

### **Types of thalassemia**

Thalassemia is classified as trait, minor, intermediate and major to describe how severe the condition is. These labels represent a range where having a thalassemia trait means that you may experience mild anemia symptoms or no symptoms at all. You may not need treatment. Thalassemia major is the most serious form and usually requires regular treatment.

There are two types of thalassemia — alpha thalassemia and beta thalassemia — named after defects in these chains.

#### **Alpha thalassemia**

You inherit four genes, two from each parent, that make alpha globin protein chains. When one or more genes are defective, you develop alpha thalassemia. The number of defective genes you inherit will determine whether you experience anemia symptoms and (if so) how severe they’ll be.

* One defective or missing alpha gene means that you won’t experience symptoms. Another name for this condition is alpha thalassemia minima.
* Two defective or missing alpha genes means that if you experience symptoms, they’ll likely be mild. Another name is alpha thalassemia minor.
* Three defective or missing alpha genes means that you’ll experience moderate to severe symptoms. Another name for this condition is Hemoglobin H disease.
* Four defective or missing alpha genes usually result in death. In those rare instances when a newborn survives, they’ll likely need lifelong blood transfusions. Another name for this condition is hydrops fetalis with Hemoglobin Barts.

#### **Beta thalassemia**

You inherit two beta-globin genes, one from each parent. Your anemia symptoms and how severe your condition is depends on how many genes are defective and which part of the beta globin protein chain contains the defect.

* One defective or missing beta gene means that you’ll experience mild symptoms. Another name for this condition is beta thalassemia minor.
* Two defective or missing beta genes means that you’ll experience moderate to severe symptoms. The moderate version is called thalassemia intermedia. More severe beta thalassemia involving two gene mutations is called beta thalassemia major or Cooley’s anemia.

### **Symptoms of thalassemia**

Your experience will depend on the type of thalassemia you have and how severe it is.

#### **Asymptomatic (no symptoms)**

You likely won’t have symptoms if you’re missing one alpha gene. If you’re missing two alpha genes or one beta gene, you may be asymptomatic. Or, you may have mild anemia symptoms, like fatigue.

#### **Mild to moderate symptoms**

Beta thalassemia intermedia may cause mild anemia symptoms, or it may cause the following symptoms associated with more moderate disease:

* Growth problems.
* Delayed puberty.
* Bone abnormalities, such as osteoporosis.
* An enlarged spleen (the organ in your abdomen that plays a part in fighting infection).

You may eventually need surgery to correct skeletal problems. Your healthcare provider may need to remove your spleen if it grows too large.

#### **Severe symptoms**

Missing three alpha genes (Hemoglobin H disease) often causes anemia symptoms at birth and leads to severe lifelong anemia. Beta thalassemia major (Cooley’s anemia) often leads to severe anemia symptoms noticeable by age 2.

Symptoms of severe anemia include those associated with mild to moderate disease. Additional symptoms may include:

* Poor appetite.
* Pale or yellowish skin (jaundice).
* Urine that’s dark or tea-colored.
* Irregular bone structure in your face.

## **Diagnosis and Tests**

Moderate and severe thalassemia are often diagnosed in childhood because symptoms usually appear within the first two years of your child’s life.

Your healthcare provider may order various blood tests to diagnose thalassemia:

* A complete blood count (CBC) that includes measures of hemoglobin and the quantity (and size) of red blood cells. People with thalassemia have fewer healthy red blood cells and less hemoglobin than normal. They may also have smaller-than-normal red blood cells.
* A reticulocyte count (a measure of young red blood cells) may indicate that your bone marrow isn’t producing enough red blood cells.
* Studies of iron will indicate whether the cause of your anemia is an iron deficiency or thalassemia.
* Hemoglobin electrophoresis is used to diagnose beta thalassemia.
* Genetic testing is used to diagnose alpha thalassemia.

## **Management and Treatment**

Standard treatments for thalassemia major are blood transfusions and iron chelation.

* A blood transfusion involves receiving injections of red blood cells through a vein to restore normal levels of healthy red blood cells and hemoglobin. You’ll receive transfusions every four months with moderate or severe thalassemia, and with beta thalassemia major, every two to four weeks. Occasional transfusions may be needed (for instance, during times of infection) for hemoglobin H disease or beta thalassemia intermedia.
* Iron chelation involves the removal of excess iron from your body. A danger with blood transfusions is that they can cause iron overload. Too much iron may damage organs. If you receive frequent transfusions, you’ll receive iron chelation therapy (which you can take as a pill).
* Folic acid supplements can help your body make healthy blood cells.
* Bone marrow and stem cell transplant from a compatible related donor is the only treatment to cure thalassemia. Compatibility means the donor has the same types of proteins, called human leukocyte antigens (HLA), on the surface of their cells as the person receiving the transplant. Your healthcare provider will inject bone marrow stem cells from your donor into your bloodstream during the procedure. The transplanted cells will start to make new, healthy blood cells within one month.
* Luspatercept is an injection that’s given every three weeks and can help your body make more red blood cells. It’s approved in the U.S. for the treatment of transfusion-dependent beta thalassemia.

### **Complications of thalassemia**

Your body may get too much iron (iron overload), either from frequent blood transfusions or the disease itself. Too much iron can cause damage to your heart, liver, and endocrine system. Your endocrine system includes glands that produce hormones that regulate processes throughout your body.

You may get frequent severe infections, especially if you receive a lot of blood transfusions. The infections may be carried in the blood you receive during a transfusion. Healthcare providers carefully screen donor blood during transfusions to prevent this from happening.

## **Outlook / Prognosis**

A bone marrow transplant from a compatible sibling offers the best chance at a cure for thalassemia. Unfortunately, most people with thalassemia lack a suitable sibling donor. Also, a bone marrow transplant is a high-risk procedure that may result in severe complications, including death.

Meet with a thalassemia specialist to determine whether you’re a candidate for a transplant. Choosing a high-volume hospital that regularly handles bone marrow transplants improves your chance of a cure while reducing your risk of complications.

### **What is the life expectancy of someone with thalassemia?**

You should expect a normal life expectancy if you have mild thalassemia. Even if your condition is moderate or severe, you have a good chance of long-term survival if you follow your treatment program (transfusions and iron chelation therapy).

Heart disease from iron overload is the leading cause of death in people with thalassemia, so keeping up with your iron chelation therapy is extremely important.

## **Prevention**

You can’t prevent thalassemia, but genetic testing can reveal whether you or your partner carry the gene. Knowing this information can help you plan your pregnancy if you plan to conceive.

Speak to a genetic counselor for guidance on family planning if you suspect you or your partner may carry gene mutations for thalassemia.

## **Living With**

You’ll need frequent complete blood counts and blood iron tests. Your healthcare provider may recommend yearly heart function and liver function tests. They may also recommend tests for viral infection (as having thalassemia increases your risk of certain serious infections). You also will need a yearly test for iron overload in your liver.

**DIFFERENTIAL DIAGNOSIS**

* **Iron deficiency anemia:** This is ruled out by iron studies and Mentzer index.
* **Anemia of chronic disease and renal failure:** Elevated markers of inflammation (CRP, ESR) point in this direction.
* **Sideroblastic anemias:** These are ruled out by iron studies and peripheral blood smear.
* **Lead poisoning:** This is ruled out by measuring serum protoporphyrin level.

**EPIDEMIOLOGY**

Alpha thalassemia is prevalent in Asian and African populations while beta-thalassemia is more prevalent in the Mediterranean population, although it is relatively common in Southeast Asia and Africa too. Prevalence in these regions may be as high as 10%. The true numbers of thalassemia affected patients in the United States are unknown, as there is no effective screening method in place

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[Thalassemia: Types, Traits, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/14508-thalassemias#overview)

**HEMOCHROMATOSIS**

**DEFINITION AND DESCRIPTION**

Hemochromatosis (he-moe-kroe-muh-TOE-sis) is a condition that causes the body to absorb too much iron from food. Excess iron is stored in the organs, especially the liver, heart and pancreas. Too much iron can lead to life-threatening conditions, such as liver disease, heart problems and diabetes.

There are a few types of hemochromatosis, but the most common type is caused by a gene change passed down through families. Only a few people who have the genes ever develop serious problems. Symptoms usually appear in midlife.

Treatment includes regularly removing blood from the body. Because much of the body's iron is contained in red blood cells, this treatment lowers iron levels.

**Symptoms**

Some people with hemochromatosis never have symptoms. Early symptoms often overlap with those of other common conditions.

Symptoms may include:

* Joint pain.
* Belly pain.
* Fatigue.
* Weakness.
* Diabetes.
* Loss of sex drive.
* Impotence.
* Heart failure.
* Liver failure.
* Bronze or gray skin color.
* Memory fog.

### **When symptoms typically appear**

The most common type of hemochromatosis is present at birth. But most people don't experience symptoms until later in life — usually after age 40 in men and after age 60 in women. Women are more likely to develop symptoms after menopause, when they no longer lose iron with menstruation and pregnancy.

### **When to see a doctor**

See a healthcare professional if you experience any of the symptoms of hemochromatosis. If you have an immediate family member who has hemochromatosis, ask your healthcare team about genetic testing. Genetic testing can check if you have the gene that increases your risk of hemochromatosis.

**Causes**

Hemochromatosis is most often caused by a change in a gene. This gene controls the amount of iron the body absorbs from food. The altered gene is passed from parents to children. This type of hemochromatosis is by far the most common type. It's called hereditary hemochromatosis.

### **Gene mutations that cause hemochromatosis**

A gene called HFE is most often the cause of hereditary hemochromatosis. You inherit one HFE gene from each of your parents. The HFE gene has two common mutations, C282Y and H63D. Genetic testing can reveal whether you have these changes in your HFE gene.

* **If you inherit two altered genes,** you may develop hemochromatosis. You also can pass the altered gene on to your children. But not everyone who inherits two genes develops problems linked to the iron overload of hemochromatosis.
* **If you inherit one altered gene,** you're unlikely to develop hemochromatosis. However, you are considered a carrier and can pass the altered gene on to your children. But your children wouldn't develop the disease unless they also inherited another altered gene from the other parent.

### **How hemochromatosis affects your organs**

Iron plays an important role in several body functions, including helping to produce blood. But too much iron is toxic.

A hormone secreted by the liver, called hepcidin, controls how iron is used and absorbed in the body. It also controls how excess iron is stored in various organs. In hemochromatosis, the role of hepcidin is affected, causing the body to absorb more iron than it needs.

This excess iron is stored in major organs, especially the liver. Over a period of years, the stored iron can cause severe damage that may lead to organ failure. It also can lead to long-lasting diseases, such as cirrhosis, diabetes and heart failure. Many people have gene changes that cause hemochromatosis. However, not everyone develops iron overload to a degree that causes tissue and organ damage.

Hereditary hemochromatosis isn't the only type of hemochromatosis. Other types include:

* **Juvenile hemochromatosis.** This causes the same problems in young people that hereditary hemochromatosis causes in adults. But iron buildup begins much earlier, and symptoms usually appear between the ages of 15 and 30. This condition is caused by changes in the hemojuvelin or hepcidin genes.
* **Neonatal hemochromatosis.** In this serious disease, iron builds up quickly in the liver of the developing baby in the womb. It is thought to be an autoimmune disease, in which the body attacks itself.
* **Secondary hemochromatosis.** This form of the disease is not inherited and is often referred to as iron overload. People with certain types of anemia or liver disease may often need multiple blood transfusions. This can lead to excess iron buildup.

**Risk factors**

Factors that increase the risk of hemochromatosis include:

* **Having two copies of an altered HFE gene.** This is the greatest risk factor for hereditary hemochromatosis.
* **Family history.** Having a parent or sibling with hemochromatosis increases the likelihood of developing the disease.
* **Ethnicity.** People of Northern European descent are more prone to hereditary hemochromatosis than are people of other ethnic backgrounds. Hemochromatosis is less common in people of Black, Hispanic and Asian ancestry.
* **Sex.** Men are more likely than women to develop symptoms of hemochromatosis at an earlier age. Because women lose iron through menstruation and pregnancy, they tend to store less of the mineral than men do. After menopause or a hysterectomy, the risk increases for women.

**Complications**

Untreated, hemochromatosis can lead to several complications. These complications especially affect the joints and organs where excess iron tends to be stored, such as the liver, pancreas and heart. Complications can include:

* **Liver issues.** Cirrhosis — permanent scarring of the liver — is just one of the complications that may happen. Cirrhosis increases the risk of liver cancer and other life-threatening complications.
* **Diabetes.** Damage to the pancreas can lead to diabetes.
* **Heart problems.** Excess iron in the heart affects the heart's ability to circulate enough blood for the body's needs. This is called congestive heart failure. Hemochromatosis also can cause irregular heart rhythms, called arrhythmias.
* **Reproductive problems.** Excess iron can lead to erectile dysfunction and loss of sex drive in men. It can cause an absence of the menstrual cycle in women.
* **Skin color changes.** Deposits of iron in skin cells can make the skin appear bronze or gray in color.

## **Diagnosis**

Hemochromatosis can be difficult to diagnose. Early symptoms such as stiff joints and fatigue may be due to conditions other than hemochromatosis.

Many people with the disease don't have any symptoms other than high levels of iron in their blood. Hemochromatosis may be identified because of irregular blood test results after testing is done for other reasons. It also may be revealed when screening family members of people diagnosed with the disease.

### **Blood tests**

The two key tests to detect iron overload are:

* **Serum transferrin saturation.** This test measures the amount of iron bound to the protein transferrin that carries iron in the blood. Transferrin saturation values greater than 45% are considered too high.
* **Serum ferritin.** This test measures the amount of iron stored in the liver. If the results of a serum transferrin saturation test are higher than usual, a healthcare professional may check serum ferritin levels.

These blood tests for iron are best performed after fasting. Elevations in one or all of these tests can be found in other disorders. You may need to have the tests repeated for the most accurate results.

### **Additional testing**

A healthcare professional may suggest other tests to confirm the diagnosis and to look for other problems:

* **Liver function tests.** These tests can help identify liver damage.
* **MRI.** An MRI is a fast and noninvasive way to measure the degree of iron overload in the liver.
* **Testing for gene changes.** Testing DNA for changes in the HFE gene is recommended if there are high levels of iron in the blood. If you're considering genetic testing for hemochromatosis, discuss the reasons for and against with your healthcare professional or a genetic counselor.
* **Removing a sample of liver tissue for testing.** If liver damage is suspected, a liver biopsy may be done. During a liver biopsy, a sample of tissue is removed from the liver using a thin needle. The sample goes to a lab to be checked for the presence of iron. The lab also looks for evidence of liver damage, especially scarring or cirrhosis. Risks of biopsy include bruising, bleeding and infection.

### **Screening healthy people for hemochromatosis**

Genetic testing is recommended for all parents, siblings and children of anyone diagnosed with hemochromatosis. If a gene change is found in only one parent, then children do not need to be tested.

**Treatment**

### **Blood removal**

Medical professionals can treat hemochromatosis safely and effectively by removing blood from the body on a regular basis. This is similar to donating blood. The process is known as phlebotomy.

The goal of phlebotomy is to lower the iron levels. The amount of blood removed and how often it's removed depend on age, overall health and the severity of iron overload.

* **Initial treatment schedule.** In the beginning, around a pint (about 470 milliliters) of blood may be taken once or twice a week — usually in a hospital or medical professional's office. While leaning back in a chair, a needle is placed into a vein in the arm. The blood flows from the needle into a tube that's attached to a blood bag. The process of removing blood is referred to as therapeutic blood removal.
* **Maintenance treatment schedule.** Once iron levels go down, blood can be removed less often, typically every 2 to 3 months. Some people may maintain typical iron levels without having any blood taken. Some may need to have blood removed monthly. The schedule depends on how quickly iron builds up in the body.

Treating hemochromatosis can help relieve symptoms of tiredness, stomach pain and skin darkening. It can help prevent serious complications such as liver disease, heart disease and diabetes. If you already have one of these conditions, phlebotomy may slow the progression of the disease. In some cases, it may even reverse it.

Phlebotomy can't reverse cirrhosis or joint pain, but it can slow the progression.

For someone with cirrhosis, a healthcare professional may recommend occasional screening for liver cancer. This usually involves an abdominal ultrasound and CT scan.

### **Chelation for those who can't undergo blood removal**

Phlebotomy may not be an option for someone who has certain conditions, such as anemia or heart complications. Instead, a healthcare professional may recommend a medicine to remove excess iron. The medicine can be injected into the body, or it can be taken as a pill. The medicine binds excess iron, allowing the body to expel iron through urine or stool in a process that's called chelation (KEE-lay-shun). Chelation is not commonly

**Lifestyle and home remedies**

In addition to therapeutic blood removal, making some lifestyle changes may further reduce the risk of complications from hemochromatosis, such as:

* **Don't take iron supplements and multivitamins containing iron.** These can increase iron levels even more.
* **Don't take vitamin C supplements.** Vitamin C increases absorption of iron. There's usually no need to restrict vitamin C in your diet, however.
* **Stay away from alcohol.** Alcohol greatly increases the risk of liver damage in people with hemochromatosis. If you have hemochromatosis and you already have liver disease, avoid alcohol completely.
* **Don't eat raw fish and shellfish.** People with hemochromatosis are at risk of infections, particularly those caused by certain bacteria in raw fish and shellfish.

Additional dietary changes generally aren't required for people receiving blood removal treatment.

## **Outlook / Prognosis**

The outlook for hemochromatosis depends on the timing of diagnosis and treatment. If not caught and addressed early, severe hemochromatosis can cause serious problems. These complications can include organ damage and possible death.

But hemochromatosis is also a manageable disease. With early detection and treatment, you can survive and live a normal, healthy life. Sometimes organ damage can even be reversed.

### **How long will I need treatment?**

Your healthcare provider will determine how long you need treatment.

If you are diagnosed with hemochromatosis, you'll need to have some blood withdrawn once a week to start. You may then be able to switch to every few months, though you’ll still need ongoing treatment.

## **Prevention**

You can’t prevent hemochromatosis, but you can get help controlling your iron levels. By identifying and treating hemochromatosis early, healthcare providers can help you avoid complications.

## **Living With**

Your healthcare provider can help you determine how much iron you need. It depends on several factors, including:

* Age.
* Pregnancy status.
* Sex.

### **Should I change my diet?**

Your healthcare provider will probably suggest that you:

* Avoid iron pills, iron injections, multivitamins containing iron and iron-fortified, processed foods.
* Avoid raw or undercooked fish and shellfish. They may contain bacteria that cause infections and complications in people with disease.
* Limit alcohol to protect your liver.
* Limit vitamin C.

### **Will my kids get hemochromatosis?**

If you have hemochromatosis (or a family history of it) and are considering having children, consider genetic testing. You and your partner can get tested for the genetic change responsible, which is called the HFE gene. Your healthcare provider and genetic counselor can help you determine the likelihood of passing it on to your children.

## **Epidemiology of Hemochromatosis**

## Prevalence and Genetic Background

* Hereditary hemochromatosis (HH) is the most common autosomal recessive genetic disorder among people of Northern European descent.
* The prevalence of HH in White populations is approximately 1 in 200 to 1 in 500 individuals.
* The most common form, type 1 HH, is primarily linked to mutations in the HFE gene, especially the C282Y mutation.
* The C282Y homozygosity prevalence is estimated at about 0.26% in populations of Northern European ancestry, with carrier frequency (heterozygotes) around 10%.
* Other mutations such as H63D and non-HFE mutations cause less common types (types 2, 3, and 4) and are found worldwide but less frequently.

## Geographic and Ethnic Distribution

* Highest prevalence in populations of Celtic, Irish, and Scandinavian ancestry.
* Less common in African, Asian, Hispanic, and Pacific Islander populations.
* The frequency of the C282Y mutation varies geographically, with marked disparities even within Europe.

## Clinical Penetrance and Diagnosis

* Despite the relatively high genetic prevalence, clinical penetrance is low and variable; only about 50% of C282Y homozygotes develop clinical features, and many remain asymptomatic.
* Diagnosis often involves blood tests (serum ferritin, transferrin saturation) and genetic testing for HFE mutations.

## Associated Morbidity and Mortality

* Untreated HH can lead to complications such as liver cirrhosis, hepatocellular carcinoma, diabetes, arthritis, and heart failure.
* Mortality associated with HH remains elevated but has improved with earlier diagnosis and treatment.

**Differential diagnoses**

Iron overload from chronic transfusion

* + Hepatitis B and C
  + Metabolic dysfunction associated steatotic liver disease (MASLD; formerly nonalcoholic fatty liver disease or NAFLD)
  + Excessive iron supplementation
  + Dysmetabolic hyperferritinemia
  + Hereditary aceruloplasminemia
  + Alcoholic liver disease
  + Porphyria cutanea tarda
  + Marrow hyperplasia
  + Hemolytic anemia
  + Biliary cirrhosis

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### 

### **von Willebrand disease**

von Willebrand disease is a common blood disorder that keeps your blood from clotting. This is an inherited disorder, meaning parents may pass the disorder on to their biological children. Healthcare providers treat this disorder with medication to help with blood clotting.

People with von Willebrand disease may bleed more than usual. For example, they may have frequent nosebleeds or bleed for a long time after getting a minor cut. Women may have heavy menstrual periods or heavy bleeding after giving birth. People who have the most serious form of von Willebrand disease may have bleeding into their joints or soft tissues that cause severe pain and swelling. Some people develop anemia.

von Willebrand disease affects 1% of the U.S. population and is the most common bleeding disorder in the United States. Globally, von Willebrand disease affects an estimated 23 to 110 in 1 million people. The numbers vary because people may have bleeding issues, but aren’t diagnosed with von Willebrand disease. In some cases, people have had bleeding issues for many years before they have a firm diagnosis.

### **Is von Willebrand disease the same as hemophilia?**

von Willebrand is similar to hemophilia but typically causes less severe symptoms.

## **Symptoms and Causes**

Many people with von Willebrand disease have the condition, but don’t have symptoms or have mild symptoms. People who have a more severe form of the condition may have the following symptoms:

* Nosebleeds: These are nosebleeds that last longer than 10 minutes and happen five or more times a year.
* Bleeding from a cut or other injury that lasts longer than 10 minutes.
* Bruises: People with von Willebrand disease bruise easily. Their bruises are raised, meaning the bruises look like they’re swollen, and their bruises are larger than a quarter.
* Iron-deficiency anemia: All anemia happens when you don’t have enough red blood cells. In iron-deficiency anemia, your body doesn’t have enough iron to make hemoglobin. Hemoglobin is the substance in your red blood cells that helps them carry oxygen.
* Post-surgery bleeding: People with von Willebrand disease may have heavy bleeding after any surgery, including dental surgery.
* Heavy periods (menstrual bleeding): This is bleeding that’s so heavy you need to change your pad or tampon every hour, or have bleeding that lasts longer than seven days.
* Heavy bleeding after childbirth or miscarriage.
* Blood in poop (stool): Blood in your poop or bleeding after pooping may be a symptom of other medical conditions. Talk to your healthcare provider if you have blood in your poop.
* Blood in pee (hematuria): Talk to your healthcare provider if you notice blood when you pee, particularly if you have an urgent need to pee and there’s blood in your pee.

### **What causes von Willebrand disease?**

von Willebrand disease is a genetic disorder that happens when certain genes mutate, or change. In von Willebrand disease, genetic mutations affect your body’s ability to make normal von Willebrand factor. Factors are proteins that help your blood to clot.

You have von Willebrand factor in your plasma, platelets and walls of your blood vessels. Plasma is the liquid part of blood. Platelets are cells that help blood clot when blood vessels rupture from injury or damage.

Normally, platelets stop bleeding by sticking to damaged blood vessels and helping to form blood clots. von Willebrand factor helps platelets stick. When you don’t have enough von Willebrand factor or you don’t have any factor, your platelets can’t stick as well as they should and it takes longer for platelets to help form blood clots.

Most people have von Willebrand disease because they inherited a mutated gene from one of their biological parents. This is autosomal dominant inheritance. Some people inherit mutated genes from both biological parents. This is autosomal recessive inheritance and is the most severe form of von Willebrand disease. People who carry the mutated gene have a 50% chance of passing the genetic mutation on to their biological children.

People also may develop von Willebrand disease as a complication of certain cancers, autoimmune disorders, heart and blood vessel diseases.

## **Diagnosis and Tests**

Your healthcare provider will ask you to describe your symptoms. They may ask if you have biological family members who have similar symptoms or bleeding disorders. They may do the following tests:

* Complete blood count (CBC): This test measures the numbers of your red blood cells, the different types of white blood cells and your platelets. It also measures the amount of hemoglobin in your red blood cells. Most people with von Willebrand disease have normal CBCs. People with unusually heavy bleeding may have low hemoglobin and red blood cell counts.
* Platelet aggregation tests: Platelets are blood cells that help blood to clot. These tests measure how well your platelets stick together so they can help make blood clots.
* Activated partial thromboplastin time test (APTT): Healthcare providers analyze other clotting factors, which, like von Willebrand factor, are proteins that help blood to clot. A lower than usual factor levels mean it takes longer for your blood to clot.
* Prothrombin time (PT): This test measures additional clotting factors.
* Fibrinogen test: Fibrinogen is another protein that helps blood to clot.
* von Willebrand factor antigen: This test measures the amount of von Willebrand factor protein in your bloodstream.
* Ristocetin cofactor: This test evaluates von Willebrand factor activity.
* von Willebrand factor multimers: This test measures the factor’s structure.

Your healthcare provider may need to do several blood tests to confirm you have von Willebrand disease. That’s because factors, including hormone levels, may change your von Willebrand factor blood levels may change.

There’s more than one type of von Willebrand disease. Healthcare providers may do more laboratory tests to identify the specific defect. Here’s more information about von Willebrand disease types:

* Type 1: This is the most common type of von Willebrand disease. It affects 60% to 80% of people with the disease. People with this type have low levels of von Willebrand factor in their blood. They may not have symptoms. If they have symptoms, those symptoms are mild.
* Type 2: In this case, von Willebrand factor doesn’t work as it should. People with this type may have mild or moderate bleeding. About 15% to 30% of people with von Willebrand disease have this type.
* Type 3: This is the most severe form of von Willebrand disease. It’s also the rarest type, affecting 5% to 10% of people with the disease. People with this type may have serious bleeding issues because they have very low von Willebrand factor levels or they don’t have any von Willebrand factor in their bloodstream.

## **Management and Treatment**

Healthcare providers may treat this condition with different medications:

* Desmopressin: This hormone boosts the levels of von Willebrand factor in your bloodstream. This is the most common treatment for von Willebrand disease.
* von Willebrand factor infusions: Some people may receive infusions of von Willebrand factor to stop bleeding episodes. They may receive this treatment before surgery. Some people with severe von Willebrand factor disease may receive regular infusions so they have a steady level of von Willebrand factor in their bloodstream.
* Antifibrinolytics: These medications keep blood clots from breaking down. Your healthcare provider may prescribe this type of medication if you’re having dental surgery or if you’re someone who has heavy periods.
* Birth control pills: This medication helps people with menstrual bleeding. It contains estrogen that increases von Willebrand factor levels in your bloodstream.

## **Outlook / Prognosis**

Healthcare providers can treat von Willebrand disease but they can’t cure it. Most people have Type 1 or Type 2 von Willebrand disease and may only need treatment if they’re injured or need surgery. People with Type 3 von Willebrand disease may need ongoing medical treatment to manage bleeding.

## **Prevention**

Most people inherit von Willebrand disease. If your biological parents have this condition, you may inherit it from one or both of them.

## **Living With**

Most people with von Willebrand disease have mild or moderate symptoms. For them, living with von Willebrand disease may mean they should:

* Avoid activities where they may get hurt, like contact sports such as football, rugby or hockey.
* Tell all healthcare providers, including their dentists, that they have the disease. That way, their healthcare providers can plan how to manage bleeding after surgery or dental surgery.
* Avoid aspirin and drugs that contain aspirin.
* Avoid nonsteroidal anti-inflammatory (NSAIDs) like ibuprofen, unless a healthcare provider who knows they have von Willebrand disease tells them to take an NSAID.
* Avoid nutritional supplement pills that contain vitamin E, fish oil or turmeric.
* Consider medical alert identification. Wearing a medical alert bracelet or carrying identification may help people get appropriate medical care in an emergency.

## **Epidemiology**

Clinically significant vWD affects approximately 125 persons per million population, with severe disease affecting approximately 0.5-5 persons per million population. Reports from screenings of unselected individuals indicated a higher prevalence of vWD abnormalities, ie, close to 1% of the population.

### Sex- and age-related demographics

Males and females are affected equally by vWD. However, the phenotype may be more pronounced in females, because of menorrhagia and the greater visibility of bruises.

In the great majority of cases, vWD is an inherited condition. Bleeding-related symptoms may occur at a young age, even just after or during birth. Some reports have suggested a decreased bleeding tendency as patients age.

## **Diagnostic Considerations**

Conditions to consider in the differential diagnosis of von Willebrand disease (vWD) include the following:

* Hemophilia A
* Hemophilia B
* Bernard-Soulier syndrome
* Platelet function defects
* Antiplatelet drug ingestion
* Fibrinolytic defects
* Platelet-type (or pseudo) vWD
* Acquired vWD

## **Differential Diagnoses**

* Factor X Deficiency
* Factor XI Deficiency
* Hemophilia A

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### **Large granular lymphocytic leukemia (LGL)**

Large granular lymphocytic leukemia (LGL) is a rare type of chronic leukemia that affects specific white blood cells known as lymphocytes. Lymphocytes fight viruses and make antibodies that help fight infection.

There are two types of large granular lymphocytic leukemia: T-cell large granular lymphocytic leukemia (T-LGL) and chronic lymphoproliferative disorder of NK cells (CLPD-NK). These conditions start in white blood cells called cytotoxic T cells or natural killer cells. Both types of large granular lymphocytic leukemia grow slowly. They typically affect people age 60 and older. Healthcare providers can treat LGL, but the condition sometimes comes back and can become a chronic health issue.

#### **How does this condition affect my body?**

LGL is a type of chronic lymphocytic leukemia that occurs when certain T cells and natural killer cells mutate, becoming abnormal cells that keep your bone marrow from producing normal blood cells. People with LGL often develop neutropenia, meaning they produce low numbers of granulocytes (the most common white blood cells) and have an increased risk of infection. They may also develop anemia, which happens because LGL cells affect red blood cell production.

Large granular lymphocytic leukemia is very rare, affecting 1 in 1 million people across the world. Most people are in their 60s when they’re diagnosed.

## **Symptoms and Causes**

People may have this condition and never have symptoms. One study showed about one-third of people with LGL didn’t have any symptoms when they were diagnosed. Instead, they learned they had LGL because blood tests showed they had unusually low red blood levels or low levels of neutrophils (a type of granulocyte). In some cases, people are diagnosed with LGL because they’re being treated for blood disorders and they have symptoms that healthcare providers link to large granular lymphocytic leukemia.

People with LGL who do have symptoms often have the following:

* Fatigue: Extreme tiredness is the most common LGL symptom and is likely due to anemia.
* Frequent fevers and recurring infections: People have fevers caused by bacterial infections.
* Enlarged spleen (splenomegaly): Infections and some types of anemia may cause your spleen to become enlarged.

#### **What conditions are linked to large granular lymphocytic leukemia?**

Many people with LGL have autoimmune diseases, particularly rheumatoid arthritis. Other common conditions are:

* Anemia: This condition means you don’t have enough healthy red blood cells and hemoglobin. Many times, people have severe anemia and rely on blood transfusions to maintain red blood cell levels. Some people with LGL have hemolytic anemia, which happens because red blood cells are destroyed and not because of low red blood cell production.
* Lymphocytosis: This is having a high lymphocyte (white blood cell) count. People who have lymphocytic leukemias or lymphomas and viral infections usually have low lymphocyte counts.

### **What causes large granular lymphocytic leukemia?**

Healthcare providers aren’t sure what causes the condition, but they believe there’s a link between this type of leukemia and immune responses, autoimmune diseases or other cancers:

* About 30% of people with this condition also have rheumatoid arthritis and other autoimmune diseases.
* Another 25% to 30% have another kind of lymphoma or other kinds of cancer.
* Many people with this condition also carry mutated forms of two genes — *STAT3* and *STAT5B* — that play roles in cell immunity and how cells divide and multiply.

## **Diagnosis and Tests**

Healthcare providers typically do blood tests and genetic analyses to diagnose this condition. Common tests may include:

* Complete blood count (CBC) with differential: A CBC with differential is a measure of all of your blood cells, including the number of each type of white blood cell.
* Peripheral blood smear: This is a technique healthcare providers use to examine blood cells under a microscope so they can count the number of LGLs in your blood.
* Flow cytometry: This lab test analyzes cell characteristics. Healthcare providers often use this test to diagnose and classify types of leukemia.
* Immunophenotyping: Healthcare providers analyze blood or tissue samples for signs of markers on cell surfaces. Markers indicate specific types of certain conditions.
* T-cell receptor (TCR) gene rearrangement analysis: Healthcare providers use these blood or bone marrow tests to look for problems in the genes that control how your T-cells work.
* Genetic testing: Healthcare providers may test for *STAT3* and *STAT5* gene mutations.

They may do other tests, including bone marrow examinations, to rule out conditions including immunodeficiency, rheumatoid arthritis, myelodysplasia and myeloid mutations. They may also check immunoglobulin levels and monoclonal protein levels.

## **Management and Treatment**

If you have T-LGL or CLPD-NK leukemia but don’t have symptoms, your provider may recommend watchful waiting. In watchful waiting, providers monitor your health, typically taking blood tests every few months and watching for signs of symptoms.

People who do have symptoms may receive immunosuppressive therapy and steroids. Healthcare providers may use one treatment after another or use low-intensity forms of treatment. Because LGL is a rare condition, people often seek out doctors who specialize in this disease.

## **Outlook / Prognosis**

Most of the time, large granular lymphocytic leukemia is a chronic illness that isn’t fatal. About 75% of people with T-LGL leukemia and CLPD-LGL leukemia are alive five years after diagnosis. About 10% of people with these types of leukemia die of severe infections that are complications of leukemia.

## **Prevention**

No, you can’t. Healthcare providers don’t know the exact cause of large lymphocytic granular leukemia, so they can’t say how you might avoid it. That said, people who have autoimmune diseases have an increased risk of developing this condition. If you have an autoimmune disease, ask your healthcare provider whether you should be concerned about developing LGL.

## **Living With**

If you have a type of large granular lymphocytic leukemia, you may not have symptoms but you should take steps like monitoring your overall health and having regular checkups. Regardless of whether you have symptoms, the following suggestions may be helpful:

* Eat a healthy diet of lean protein, fruits, vegetables and whole grains.
* Exercise regularly.
* Get enough rest.
* Manage your stress.
* Protect your immune system: Ask your provider about vaccinations and other things you should do to avoid infection.

### **Can you live a normal life with this condition?**

In general, people treated for LGL can typically live normal lives and have the same lifespan as people who don’t have the condition. It’s important to remember that some people who have LGL already have serious blood disorders that affect their quality of life.

### **When should I see my healthcare provider?**

You should see your healthcare provider if you develop symptoms that may be signs your condition is getting worse. If you have symptoms and are receiving treatment, you should see your provider if you notice changes in your body, such as symptoms that are getting worse.

### **What questions should I ask my healthcare provider?**

Large granular lymphocytic leukemia is a very rare illness. Here are some suggested questions that may help you learn more about LGL:

* What type of LGL do I have?
* What are treatments?
* Will I need more than one kind of treatment?
* I feel fine. Will I have symptoms?
* I have other medical conditions. Will LGL make them worse?

**Differential diagnosis (DDX) of Large Granular Lymphocytic (LGL) leukemia**

* Reactive LGL lymphocytosis  
  Occurs secondary to viral infections (e.g., CMV, EBV, HIV), bone marrow transplants, solid malignancies, or other non-Hodgkin lymphomas. These reactive LGLs are usually polyclonal and subside when the underlying condition resolves, unlike the clonal proliferation in LGL leukemia.
* Other lymphoproliferative disorders  
  Including Non-Hodgkin's lymphomas and post-transplant lymphoproliferative disorders, which may feature increased LGLs but have distinct clinical and pathological characteristics.
* Felty syndrome  
  Characterized by neutropenia, splenomegaly, and rheumatoid arthritis, it can overlap clinically and immunophenotypically with T-cell LGL leukemia, as both involve clonal expansions of cytotoxic T cells bearing CD16 and CD57 markers.
* Autoimmune diseases  
  Many patients with LGL leukemia have associated autoimmune disorders, especially rheumatoid arthritis, which can confound diagnosis.
* Chronic lymphoproliferative disorder of NK cells (CLPD-NK)  
  A subtype of LGL leukemia with chronic NK-cell proliferation, distinguished by immunophenotyping (CD3-negative, CD16+, CD56+) and genetic markers.
* Aggressive NK-cell leukemia  
  A more acute and aggressive form with systemic involvement, differing from the chronic forms of LGL leukemia

**Epidemiology of Large Granular Lymphocytic (LGL) Leukemia:**

* Rarity: LGL leukemia is a rare lymphoproliferative disorder, accounting for about 2-5% of chronic lymphoproliferative diseases in the US and Europe, and slightly higher (5-6%) in Asian populations.
* Incidence: The annual incidence is approximately 0.2 cases per 1,000,000 individuals in the US and Europe. Some studies report an incidence rate of about 0.14 to 0.2 per 100,000 individuals, with variation depending on population studied.
* Age: It primarily affects middle-aged to elderly adults, with a median age at diagnosis between 55 and 67 years. Females tend to be diagnosed slightly earlier than males (by about 2-3 years). Around 14-26% of patients are diagnosed before age 50.
* Sex distribution: The incidence is roughly equal between males and females, with no strong sex predilection overall, though some studies report a slightly higher incidence in males.
* Ethnicity: The aggressive NK-cell variant of LGL leukemia is more common in Asian populations (Japanese, Korean, Taiwanese), often presenting at a younger age by a decade or two compared to Western populations. Overall incidence rates do not differ significantly among racial groups in the US.
* Associated conditions: LGL leukemia is frequently associated with autoimmune diseases such as rheumatoid arthritis, which complicates precise incidence estimates due to overlapping treatments and diagnoses.
* Survival: The 5-year overall survival ranges from about 77% to 82%, with better outcomes in females and non-Caucasian ethnicities

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[Large Granular Lymphocytic Leukemia: Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/24128-large-granular-lymphocytic-leukemia)

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### **Autoimmune hemolytic anemia**

Autoimmune hemolytic anemia (AIHA) occurs when your immune system mistakes red blood cells as unwanted substances. As a result, your body produces antibodies that destroy red blood cells, which can lead to a low amount of red blood cells (known as anemia).

AIHA is highly manageable, but it can be fatal if left untreated. Immediate intervention is essential.

### **primary and secondary autoimmune hemolytic anemia**

If your AIHA develops without the obvious presence of an underlying condition, it’s called primary AIHA.

Secondary AIHA is when it’s linked to another condition, such as a viral illness, other autoimmune diseases, medication or underlying blood cancer (such as lymphoma).

### **Types of autoimmune hemolytic anemia**

There are two main types of autoimmune hemolytic anemia: warm autoimmune hemolytic anemia and cold autoimmune hemolytic anemia. This classification depends on the type of antibodies involved in the disease.

#### **Warm autoimmune hemolytic anemia**

The most common type of AIHA, warm autoimmune hemolytic anemia, involves IgG antibodies, which bind red blood cells at normal body temperature. Generally, symptoms occur gradually over the course of several weeks. In some cases, however, they can develop within days.

#### **Cold autoimmune hemolytic anemia**

Affecting 10% to 20% of cases, cold autoimmune hemolytic anemia involves IgM autoantibodies. These bind red blood cells when your blood is at cooler temperatures compared to your body’s core temperature. There’s a wide variation in the temperature threshold at which a cold autoantibody will bind to red blood cells.

### **Who does autoimmune hemolytic anemia affect?**

AIHA can affect people of all ages and genders, though it most commonly occurs in females over the age of 40.

Autoimmune hemolytic anemia is rare, affecting approximately 1 to 2 out of every 100,000 people each year.

## **Symptoms and Causes**

AIHA can result in a wide range of symptoms, including:

* Fever.
* Tiredness.
* Weakness.
* Rapid heartbeat.
* Shortness of breath.
* Paleness.
* Jaundice (yellowing skin).
* Headaches.
* Muscle pain.
* Dark pee.
* Nausea and vomiting.
* Difficulty breathing.
* Diarrhea.
* A sore tongue.
* Heart palpitations.

Many symptoms are specific to the type of AIHA you have.

For example, warm autoimmune hemolytic anemia most commonly causes:

* Tiredness.
* Dizziness.
* Jaundice (yellowing skin).
* Heart palpitations.

Cold autoimmune hemolytic anemia symptoms often include:

* Tiredness.
* Dizziness.
* Cold hands and feet.
* Jaundice.
* Chest pain.
* Pain in the backs of your legs.
* Raynaud’s disease.
* Blue coloring in your hands and feet.
* Arrhythmia.
* Heart murmur.
* Heart failure.

### **What causes autoimmune hemolytic anemia?**

In approximately half of all cases, autoimmune hemolytic anemia causes are unknown (idiopathic autoimmune hemolytic anemia). In other cases, there’s a link between AIHA and other disorders.

#### **What disorders can cause autoimmune hemolytic anemia?**

There are several autoimmune diseases associated with secondary AIHA. They include:

* Lupus.
* Rheumatoid arthritis.
* Sjogren’s syndrome.
* Thyroid disease.
* Ulcerative colitis.
* Hashimoto’s disease.

Sometimes, viruses can cause AIHA to develop, though the anemia goes away once the infection is treated. Common viruses that may be linked to AIHA include:

* Epstein-Barr virus.
* Measles.
* Mumps.
* Rubella.
* Atypical pneumonia.
* Varicella, the virus that causes chickenpox.
* HIV.
* Hepatitis.
* Cytomegalovirus.

Medications associated with AIHA include:

* Antibiotics.
* Nonsteroidal anti-inflammatory drugs (NSAIDs).
* Anti-cancer drugs.

## **Diagnosis and Tests**

Your healthcare provider will recommend a complete blood count (CBC) to look for warning signs of anemia. Specifically, this test measures:

* How many red blood cells, white blood cells and platelets you have.
* The size of your red blood cells.
* Hemoglobin, the protein in your blood that carries oxygen throughout your body.
* Hematocrit (how much space your red blood cells take up in your blood).

If your healthcare provider suspects anemia, they might order additional tests. These assessments may include:

* Peripheral smear. Your healthcare provider examines a sample of your blood under a microscope to see if your blood cells are being destroyed.
* Reticulocyte count. This test measures how many young red blood cells are in your body. If your bone marrow is making a lot more cells to replace the destroyed ones, then your reticulocyte count will be high.
* Bilirubin test. Bilirubin increases when red blood cells are destroyed.
* Coombs’ test. Your healthcare provider will run this test to determine if your body is making antibodies against red blood cells.
* Haptoglobin test. Haptoglobin is a protein that eliminates debris produced by damaged red blood cells. If your body is using up a lot of haptoglobin, your levels will be low.
* Lactate dehydrogenase (LDH). Lactate dehydrogenase is an enzyme that’s present in red blood cells. When red blood cells are destroyed, the LDH level will rise.
* Cold agglutinin titer. If your healthcare provider suspects cold autoimmune hemolytic anemia, they may perform this test. It tells your healthcare provider the level of antibodies that attack red blood cells at cold temperatures.

## **Management and Treatment**

Autoimmune hemolytic anemia treatment usually involves addressing underlying conditions first. For example, if your AIHA is linked to lupus, then your healthcare provider will probably start by treating the lupus directly. If AIHA is caused by lymphoma, treating the lymphoma directly is important. If AIHA is associated with a certain drug, you’ll likely stop taking that medication. In addition, people with mild AIHA may not need treatment at all.

#### **Medications**

Corticosteroids help weaken your body’s immune response. That’s why they’re typically the first line of treatment for autoimmune hemolytic anemia. If corticosteroids don’t work, then your healthcare provider may prescribe immunosuppressants. The goal is to stop your immune system from attacking your bone marrow.

#### **Splenectomy**

When medications don’t work, you may need surgery to remove your spleen. Your spleen is responsible for eliminating abnormal red blood cells from your bloodstream, including those with antibodies. The spleen also houses antibody-producing cells. A splenectomy can help preserve red blood cells, reducing the risk of anemia.

#### **Blood transfusion**

In severe cases, people with AIHA may need a blood transfusion.

### **Are warm and cold autoimmune hemolytic anemia treated differently?**

Primary cold autoimmune hemolytic anemia is treated differently from warm autoimmune hemolytic anemia. Medications that work for warm autoimmune hemolytic anemia include corticosteroids or immunosuppressants. If that approach doesn’t work, then you may need a splenectomy. Blood transfusions are considered in the situation of severe anemia as supportive care while the disease is being treated.

Cold autoimmune hemolytic anemia doesn’t respond well to corticosteroids or splenectomy. In a mild case of cold autoimmune hemolytic anemia, keeping warm by using hand/feet warmers, gloves, socks or even moving to a warmer climate may be enough to keep the disease at bay. When treatment is needed, rituximab with or without other immunosuppressive agents is the first line of therapy.

## **Outlook / Prognosis**

Autoimmune hemolytic anemia can be so mild you don’t need treatment. But it can also be so advanced that you require surgery or a blood transfusion. If you’ve been diagnosed with AIHA, your healthcare provider can talk with you about the severity of your diagnosis and your treatment options.

### **Can autoimmune hemolytic anemia be cured?**

Yes. Most people with AIHA only need minimal treatment, if any. About 20% to 30% of people require medication, surgery or a blood transfusion.

It’s important to note that AIHA can be fatal if left untreated. That’s why immediate intervention is so important.

## **Prevention**

It’s not always possible to prevent autoimmune hemolytic anemia. But if you have a viral infection or use medications that are commonly linked to AIHA, then your healthcare provider can monitor your situation in an effort to reduce your risk of developing the condition.

### **When should I see my healthcare provider?**

If you start showing anemia symptoms — such as fatigue, weakness, jaundice or shortness of breath — schedule an appointment with your healthcare provider right away.

**Differential diagnosis (DDX) of autoimmune hemolytic anemia (AIHA)**

Cold agglutinin disease (CAD)  
A subtype of AIHA caused by IgM antibodies active at cold temperatures; distinguished by cold-reactive antibodies and complement-mediated hemolysis.

* Paroxysmal cold hemoglobinuria (PCH)  
  A rare autoimmune hemolytic anemia caused by biphasic Donath-Landsteiner antibodies; typically presents with intravascular hemolysis triggered by cold exposure.
* Microangiopathic hemolytic anemia (MAHA)  
  Includes thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC); characterized by schistocytes on blood smear and often thrombocytopenia.
* Paroxysmal nocturnal hemoglobinuria (PNH)  
  A clonal hematopoietic stem cell disorder causing complement-mediated intravascular hemolysis; diagnosed by flow cytometry detecting CD55/CD59 deficiency.
* Hereditary spherocytosis and other membrane defects  
  Congenital hemolytic anemias with spherocytes on smear but negative direct antiglobulin test (DAT).
* Glucose-6-phosphate dehydrogenase (G6PD) deficiency  
  An enzymopathy causing episodic hemolysis triggered by oxidative stress; negative DAT.
* Hemoglobinopathies (e.g., sickle cell disease, thalassemias)  
  Chronic hemolytic anemias with characteristic hemoglobin electrophoresis findings.
* Drug-induced immune hemolytic anemia  
  Caused by antibodies triggered by certain medications; may mimic AIHA but often resolves with drug cessation.
* Infections  
  Viral (e.g., Epstein-Barr virus, Mycoplasma pneumoniae) or bacterial infections can cause hemolysis or trigger AIHA.
* Malignancies and lymphoproliferative disorders  
  Such as chronic lymphocytic leukemia (CLL), which can be associated with secondary AIHA.
* Other autoimmune diseases  
  Systemic lupus erythematosus (SLE) and other connective tissue diseases can cause secondary AIHA.

**Epidemiology of Autoimmune Hemolytic Anemia (AIHA):**

* Incidence: AIHA is a rare disorder with an estimated incidence of 1 to 3 cases per 100,000 population per year. Some sources specify an incidence range from about 1/35,000 to 1/80,000 annually in North America and Western Europe.
* Prevalence: The point prevalence varies but is generally low, consistent with its rarity. Cold agglutinin disease (a subtype of AIHA) has a prevalence of approximately 14 to 33 per 1,000,000.
* Age distribution: AIHA can occur at any age but is more common in middle-aged and older adults, with a median age at diagnosis around 60-70 years. Pediatric cases are less frequent.
* Sex distribution: There is a slight female predominance, with females representing about 60-66% of cases.
* Types:
  + Warm AIHA accounts for about 60-70% of cases.
  + Cold AIHA (including cold agglutinin disease) accounts for 13-15%.
  + Mixed-type and drug-induced AIHA are less common.
* Secondary AIHA: Approximately half of warm AIHA cases are secondary to other conditions such as autoimmune diseases (e.g., systemic lupus erythematosus), lymphoproliferative disorders (e.g., chronic lymphocytic leukemia), infections, or drugs.
* Mortality: Mortality rates vary between 3% and 20% depending on cohort and severity, with infections and complications being common causes of death

REFERENCES

[Autoimmune Hemolytic Anemia: Treatment, Symptoms & Types](https://my.clevelandclinic.org/health/diseases/22349-autoimmune-hemolytic-anemia#overview)

### 

### **Hemolytic anemia**

Hemolytic anemia is a blood disorder that makes your red blood cells break down or die faster than your body can replace them with new blood cells. People may develop hemolytic anemia due to genetic conditions that cause anemia. Sometimes, people have mild hemolytic anemia symptoms that go away after treatment. Many times, healthcare providers can cure hemolytic anemia after finding out what caused the condition. Left untreated, however, severe hemolytic anemia can cause serious heart trouble.

### **What type of anemia is hemolytic anemia?**

There are many different types of anemia. Hemolytic anemia happens when your red blood cells break down or die faster than they usually do. Red blood cells normally live for about 120 days. When they break down or die sooner than that, your bone marrow doesn’t have time to produce enough new red blood cells, leaving you with a low red blood cell count. Other anemia types may occur when:

* Injury or illness causes excessive bleeding that drains your red blood cell supply faster than your body can replace it.
* Something affects red blood cell production so your body either produces fewer red blood cells or produces abnormal red blood cells.

Hemolytic anemia is less common than anemia caused by excessive bleeding or slow red blood cell production.

### **What happens if hemolytic anemia is not treated?**

Severe hemolytic anemia can lead to serious heart conditions, including arrhythmia (abnormal heart rhythm), cardiomyopathy and heart failure.

There are several kinds of hemolytic anemia, and each of these may affect people of all age groups, races and genders.

### **Hemolytic anemia and autoimmune hemolytic anemia**

Autoimmune hemolytic anemia (AIHA) occurs when your immune system mistakes red blood cells for unwanted or foreign substances. Your body reacts by producing antibodies that destroy the red blood cells, causing anemia. Different factors may cause hemolytic anemia, including inherited conditions, infections and some medications.

## **Symptoms and Causes**

Hemolytic anemia may be caused by inherited conditions that affect the red blood cells. It’s also caused by certain infections or if someone receives a blood transfusion from a donor whose blood type didn’t match.

### **What inherited conditions can cause hemolytic anemia?**

Some common inherited conditions are:

* Sickle cell anemia: In this disease, your body produces abnormally shaped red blood cells that are trapped in small blood vessels, your spleen or liver.
* Thalassemia: This is another group of inherited blood disorders that cause your body to make abnormal red blood cells that are easily destroyed.
* G6PD deficiency: This genetic disorder affects an enzyme that protects red blood cells. When this enzyme level drops, blood cells exposed to certain infections or medications are likely to break apart.

### **What infections may cause hemolytic anemia?**

Infections linked to hemolytic anemia include:

* Malaria:This disease happens when mosquitoes infected with tiny malaria parasites bite people, leaving parasites in people's bloodstreams. Left untreated, malaria can cause hemolytic anemia.
* Rocky Mountain spotted fever: This infection spreads when ticks infected with the bacteria *Rickettsia rickettsi* bite people.
* Haemophilus influenza disease:These are infections caused by the bacteria *H. influenza.*
* Human immunodeficiency virus (HIV): This virus causes acquired immunodeficiency syndrome (AIDS).

### **What medications may cause hemolytic anemia?**

Some people develop hemolytic anemia from taking certain medications. Not everyone who takes these medications will develop hemolytic anemia. Your healthcare provider will review your medical history and current problems to be sure you can take these medications. These medications include:

* Penicillin: This antibiotic treats infections and other serious medical problems.
* Quinine: This medication treats malaria.
* Methyldopa: This medication treats high blood pressure.
* Sulfonamides: This is an anti-bacterial medication.

### **What are hemolytic anemia symptoms?**

Hemolytic symptoms can be mild or more severe. They also can come on suddenly or develop over time. Typical symptoms include:

* Jaundice: This condition affects your skin, the whites of your eyes (sclera) and your mucous membranes, causing them to turn yellow. This happens when you have a high level of bilirubin caused by a breakdown of your red blood cells.
* Shortness of breath (dyspnea): This happens when you don’t have enough red blood cells carrying oxygen throughout your body.
* Fatigue: Fatigue is a sensation of being so tired that it affects your daily life and your ability to do your daily activities.
* Fast heartbeat (tachycardia): This condition means your heart is beating faster than it should. When your heart beats too fast, it doesn’t have enough time between beats to fill up with blood, and your heart can’t supply your body with the oxygen it needs.
* Low blood pressure (hypotension): Low blood pressure can be a symptom or a condition. It happens when your blood pressure is much lower than expected.
* Blood in your pee (hematuria): This can be a symptom of sickle cell disease.
* Enlarged spleen or liver: Your liver and spleen filter red blood cells as the cells move through your body. Red blood cells that are damaged or dying are trapped by your spleen and liver, which destroy the cells. A larger-than-normal spleen or liver may be a sign your red blood cells are damaged.

### **Can anemia be a medical emergency?**

Acute anemia may be a symptom of sudden and severe loss of blood or a sign that red blood cells are being destroyed very quickly. People who have acute anemia may have the following symptoms:

* They’re very weak.
* Their hearts are beating very hard and fast.
* They have trouble catching their breath.

## **Diagnosis and Tests**

Healthcare providers diagnose hemolytic anemia by:

* Asking about your medical history, specifically if your family members have anemia.
* Asking if you have certain infections or are taking certain medications that may cause hemolytic anemia.
* Doing a physical examination focused on anemia signs and symptoms, jaundice or if your spleen or liver is enlarged.

Healthcare providers typically use several blood tests to diagnose hemolytic anemia. They may also examine blood samples for genetic markers that may be signs of inherited conditions that cause hemolytic anemia. Typically, they’ll do preliminary blood tests to determine if your symptoms are caused by some form of anemia. A complete blood count (CBC) is one of the preliminary tests they may do. A CBC measures:

* How many red blood cells, white blood cells and platelets you have.
* The size of your red blood cells.
* Hemoglobin, the protein in your blood that carries oxygen throughout your body.
* Hematocrit, which measures the amount of space your red blood cells take in your blood.

### **What are the other tests healthcare providers may do?**

They may order additional tests to identify the kind of anemia you may have. Here are tests that providers use to diagnose anemia, including hemolytic anemia:

* Coombs test (direct antiglobulin test):This test checks for autoimmune hemolytic anemia.
* Reticulocyte count: A reticulocyte count measures the number of immature red blood cells (reticulocytes) in your bone marrow. Healthcare providers measure reticulocytes to find out if your bone marrow is producing enough healthy red blood cells.
* Haptoglobin test:Haptoglobin is a protein that eliminates debris produced by damaged red blood cells. Low haptoglobin levels may be a sign of damaged red blood cells.
* Lactate dehydrogenase (LDH):LDH is an enzyme in red blood cells. A high LDH level may be a sign of increased red blood cell destruction.
* Unconjugated bilirubin:When your red blood cells break down, they make bilirubin. This test measures the amount of bilirubin that’s not being processed by your liver. This is unconjugated bilirubin. A high unconjugated bilirubin level may be a sign that large numbers of red blood cells are being destroyed.
* Peripheral blood smear:Healthcare providers examine blood cells for signs of abnormalities, including size and shape.
* Hemoglobin electrophoresis:Healthcare providers use this test to analyze hemoglobin, a protein in your red blood cells that helps cells carry oxygen throughout your body.

## **Management and Treatment**

Healthcare providers treat hemolytic anemia based on the cause of your illness and if you’re having severe symptoms. For example, if your healthcare provider believes you have severe anemia, they may order blood transfusions to stabilize your red blood cell count. Then they’ll diagnose the underlying condition that’s causing you to have anemia so they can treat the condition.

## **Outlook / Prognosis**

Hemolytic anemia affects people in different ways. Sometimes, hemolytic anemia is a symptom of an underlying serious medical condition that requires extensive treatment. Other times, hemolytic anemia happens as a reaction to certain infections and medications. In those cases, healthcare providers cure the condition by treating the underlying infection or changing medications.

## **Prevention**

Hemolytic anemia may be caused by several factors, most of which you can’t control. For example, you can develop hemolytic anemia after being injured, or by inheriting certain conditions. You can, however, reduce your risk for serious illness by talking to your healthcare provider any time you develop symptoms that may be anemia.

## **Living With**

Healthcare providers may be able to cure your hemolytic anemia. Once you’re feeling better, you may be interested in learning how to manage your health to avoid another bout of illness. Some suggestions that may help you to manage anemia include:

* Follow a healthy diet rich in vitamins B12, C and B9 (folic acid). Ask to speak to a nutritionist if you’d like more information on ways to keep your red blood cells strong.
* Drink enough water to stay hydrated.
* Get regular exercise. Check with your healthcare provider about ways to exercise safely.
* Avoid infections by washing your hands and avoiding people when they’re sick.
* Keep track of your symptoms by writing them down.
* Talk to your doctor about any changing symptoms.

## **Epidemiology**

Hemolytic anemia represents approximately 5% of all anemias. Acute AIHA is relatively rare, with an incidence of one to three cases per 100,000 population per year.

A review of the Nationwide Inpatient Sample database found that the prevalence of nonimmune hemolytic anemia was 0.17% in all hospitalized patients with alcoholic liver disease. The presence of anemia among inpatients with alcoholic liver disease was associated with a significantly worse prognosis, including longer average length of stay (8.8 vs 6.0 days), increased hospital charges ($38,961 vs $25,244), and higher mortality (9.0% vs 5.6%).

Hemolytic anemias are not specific to any race. However, sickle cell disorders are found primarily in Africans, African Americans, some Arabic populations, and Aborigines in southern India.

Several variants of G6PD deficiency exist. The A(-) variant is found in West Africans and African Americans. Approximately 10% of African Americans carry at least 1 copy of the gene for this variant. The Mediterranean variant occurs in individuals of Mediterranean descent and in some Asians.

Most cases of hemolytic anemia are not sex specific. However, AIHA is slightly more likely to occur in females than in males. G6PD deficiency is an X-linked recessive disorder and therefore primarily males are affected while females are more commonly carriers.

Although hemolytic anemia can occur in persons of any age, hereditary disorders are usually evident early in life. AIHA is more likely to occur in middle-aged and older individuals.

## **Diagnostic Considerations**

Other causes for fatigue, tachycardia, and dyspnea should be considered. Other causes for anemia should be ruled out. Need for transfusion in the absence of blood loss or bone marrow aplasia would suggest hemolysis.

## **Differential Diagnoses**

* Disseminated Intravascular Coagulation (DIC)
* Physical Medicine and Rehabilitation for Systemic Lupus Erythematosus
* Thrombotic Thrombocytopenic Purpura (TTP)

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**MYELODYSPLASTIC SYNDROME**

**DEFINITION AND DESCRIPTION**

Myelodysplastic syndromes are a group of disorders caused by blood cells that are poorly formed or don't work properly. Myelodysplastic syndromes result from something amiss in the spongy material inside your bones where blood cells are made (bone marrow).

Management of myelodysplastic syndromes is most often intended to slow the disease, ease symptoms and prevent complications. Common measures include blood transfusions and medications to boost blood cell production. In certain situations, a bone marrow transplant, also known as a stem cell transplant, may be recommended to replace your bone marrow with healthy bone marrow from a donor.

**Causes**

In a healthy person, bone marrow makes new, immature blood cells that mature over time. Myelodysplastic syndromes occur when something disrupts this process so that the blood cells don't mature.

Instead of developing normally, the blood cells die in the bone marrow or just after entering the bloodstream. Over time, there are more immature, defective cells than healthy ones, leading to problems such as fatigue caused by too few healthy red blood cells (anemia), infections caused by too few healthy white blood cells (leukopenia) and bleeding caused by too few blood-clotting platelets (thrombocytopenia).

Most myelodysplastic syndromes have no known cause. Others are caused by exposure to cancer treatments, such as chemotherapy and radiation, or to toxic chemicals, such as benzene.

### **Types of myelodysplastic syndromes**

The World Health Organization divides myelodysplastic syndromes into subtypes based on the type of blood cells — red cells, white cells and platelets — involved.

Myelodysplastic syndrome subtypes include:

* **Myelodysplastic syndromes with single-lineage dysplasia.** One blood cell type — white blood cells, red blood cells or platelets — is low in number and appears abnormal under the microscope.
* **Myelodysplastic syndromes with multilineage dysplasia.** In this subtype, two or three blood cell types are abnormal.
* **Myelodysplastic syndromes with ring sideroblasts.** This subtype involves a low number of one or more blood cell types. A characteristic feature is that existing red blood cells in the bone marrow contain rings of excess iron.
* **Myelodysplastic syndromes with isolated del(5q) chromosome abnormality.** People with this subtype have low numbers of red blood cells, and the cells have a specific mutation in their DNA.
* **Myelodysplastic syndromes with excess blasts.** In this subtype, any of the three types of blood cells — red blood cells, white blood cells or platelets — might be low and appear abnormal under a microscope. Very immature blood cells (blasts) are found in the blood and bone marrow.
* **Myelodysplastic syndromes, unclassifiable.** In this subtype, there are reduced numbers of one or more types of mature blood cells and the cells might look abnormal under the microscope. Sometimes the blood cells appear normal, but analysis might find that the cells have DNA changes that are associated with myelodysplastic syndromes.

**Risk factors**

Factors that can increase your risk of myelodysplastic syndromes include:

* **Older age.** Most people with myelodysplastic syndromes are older than 60.
* **Previous treatment with chemotherapy or radiation.** Chemotherapy or radiation therapy, both of which are commonly used to treat cancer, can increase your risk of myelodysplastic syndromes.
* **Exposure to certain chemicals.** Chemicals, including benzene, have been linked to myelodysplastic syndromes.

**Complications**

Complications of myelodysplastic syndromes include:

* **Anemia.** Reduced numbers of red blood cells can cause anemia, which can make you feel tired.
* **Recurrent infections.** Having too few white blood cells increases your risk of serious infections.
* **Bleeding that won't stop.** Lacking platelets in your blood to stop bleeding can lead to excessive bleeding.
* **Increased risk of cancer.** Some people with myelodysplastic syndromes might eventually develop a cancer of the bone marrow and blood cells (leukemia).

**Symptoms**

People with myelodysplastic syndromes might not experience signs and symptoms at first.

In time, myelodysplastic syndromes might cause:

* Fatigue
* Shortness of breath
* Unusual paleness (pallor), which occurs due to a low red blood cell count (anemia)
* Easy or unusual bruising or bleeding, which occurs due to a low blood platelet count (thrombocytopenia)
* Pinpoint-sized red spots just beneath the skin that are caused by bleeding (petechiae)
* Frequent infections, which occur due to a low white blood cell count (leukopenia)

### **When to see a doctor**

Make an appointment with your doctor if you have signs or symptoms that worry you.

## **Diagnosis**

A physical exam, medical history and tests might be used if your doctor suspects that you have myelodysplastic syndrome.

Tests might include:

* **Blood tests.** Your doctor might order blood tests to determine the number of red cells, white cells and platelets and look for unusual changes in the size, shape and appearance of various blood cells.
* **Removing bone marrow for testing.** During a bone marrow biopsy and aspiration, a thin needle is used to withdraw (aspirate) a small amount of liquid bone marrow, usually from a spot on the back of your hip bone. Then a small piece of bone with its marrow is removed (biopsy).

Blood and bone marrow samples are sent for laboratory analysis. Specialized tests can determine the specific characteristics of your cells that will be helpful for determining the type of myelodysplastic syndrome you have, your prognosis and your treatment options.

**Treatment**

Management of myelodysplastic syndromes is most often intended to slow the disease, ease symptoms and prevent complications. There's no cure for myelodysplastic syndromes, but some medications can help slow the progression of the disease.

If you have no symptoms, treatment might not be needed right away. Instead, your doctor might recommend regular exams and lab tests to monitor your condition and to see if the disease progresses.

Research on myelodysplastic syndromes is ongoing. Ask your doctor about clinical trials for which you might be eligible.

### **Blood transfusions**

Blood transfusions with healthy blood cells from donors can be used to replace red blood cells and platelets in people with myelodysplastic syndromes. Blood transfusions can help control symptoms.

### **Medications**

Treatment for myelodysplastic syndromes might include medications that:

* **Increase the number of blood cells your body makes.** Called growth factors, these medications are artificial versions of substances found naturally in your bone marrow. Growth factors that stimulate your bone marrow to make more red blood cells can help reduce your need for frequent blood transfusions. Growth factors that promote white blood cell production may reduce your risk of infection.
* **Stimulate blood cells to mature.** Medications that help stimulate the blood cells to mature can reduce the need for frequent blood transfusions in people who aren't helped by growth factors. Some of these drugs may also reduce the risk that the disease may progress to leukemia.
* **Suppress your immune system.** Medications that suppress or control your immune system are used in certain myelodysplastic syndromes to reduce your need for red blood cell transfusions.
* **Help people with a certain genetic abnormality.** If your myelodysplastic syndrome is associated with a gene mutation called isolated del(5q), your doctor might recommend lenalidomide (Revlimid).
* **Treat infections.** If your condition causes you to have infections, you'll receive treatments to control them.

### **Bone marrow transplant**

A bone marrow transplant, also known as a stem cell transplant, is the only treatment option that offers the potential of a cure for myelodysplastic syndromes. But this treatment carries a high risk of serious complications and it's generally reserved for people who are healthy enough to endure it.

During a bone marrow transplant, high doses of chemotherapy drugs are used to clear out the defective blood cells from your bone marrow. Then the abnormal bone marrow stem cells are replaced with healthy, donated cells (allogeneic transplant).

In some situations, less intense chemotherapy drugs can be used to reduce the risks of bone marrow transplant for older adults and those who might not otherwise be considered for this treatment.

**Lifestyle and home remedies**

Because people with certain myelodysplastic syndromes have low white blood cell counts, they're subject to recurrent, and often serious, infections.

To reduce your risk of infections:

* **Wash your hands.** Wash hands frequently and thoroughly with warm, soapy water, especially before eating or preparing food. Carry an alcohol-based hand sanitizer for times when water isn't available.
* **Take care with food.** Thoroughly cook all meat and fish. Avoid fruits and vegetables you can't peel, especially lettuce, and wash all produce you do use before peeling it. To increase safety, you might want to avoid all raw foods.
* **Avoid people who are ill.** Try to avoid close contact with anyone who is sick, including family members and co-workers

**Epidemiology**

The actual incidence of MDS in the United States is unknown. MDS was first considered a separate disease in 1976, and its occurrence was estimated at 1500 new cases every year. At that time, only patients with less than 5% blasts were considered to have this disorder. MDS was not classified as neoplastic and included in cancer registries until 2001. Current estimates of the incidence of MDS in the United States vary widely, from 10,000 to 30,000-55,000 new cases each year. The higher figures have been questioned as possible overestimates resulting from inclusion of other hematopoietic conditions.

The incidence of MDS has appeared to be increasing. The apparent rise is believed to reflect the increase in the elderly population, but may also reflect improvements in recognition and criteria for the diagnosis.

Although MDS may occur in persons of any age, including children, MDS primarily affects elderly people, with the median onset in the seventh decade of life. Data from 2001 through 2003 of the first National Cancer Institute's Surveillance, Epidemiology & End Reports (SEER) indicate 86% of MDS cases were diagnosed in individuals who were 60 years of age or older (median age: 76y).

Other data from SEER also show that the estimated incidence of MDS increases significantly with age, ranging from 0.7 per 100,000 population during the fourth decade of life to 20.8-36.3/100,000 after age 70 years. There is a fivefold difference in risk between age 60 and ≥80 years.

At all ages, MDS is more common in males than in females. In SEER data from 2001-2003, the incidence rate was significantly higher in men than in women (4.5 vs 2.7 per 100,000 population).

MDS is found worldwide and is similar in characteristics throughout the world. Data based mainly on European numbers from Germany and Sweden were very similar to the US numbers.

A review of United Kingdom population-based data from September 2004 to August 2013 found marked variations in MDS incidence, depending on the standard population used to calculate rates. For example, using the 1996 world standard, the population with the greatest weighting towards younger groups, the incidence rate was 1.67 per 100,000 population; using the 2013 European Standard Population, which has the greatest weighting towards older ages, the rate was 4.4 per 100,000 population.

## **Diagnostic Considerations**

Myelodysplastic syndrome (MDS) is typically diagnosed by finding some combination of dysplastic cell morphology, increased marrow blasts, and a karyotypic abnormality. Other causes of cytopenias must be excluded. Common etiologies of cytopenias or morphologic abnormalities that may mimic MDS include the following:

* Medication (eg, methotrexate)
* Deficiencies of cobalamin, folate, or copper
* Alcohol abuse
* HIV infection
* Immune-mediated cytopenias (eg, aplastic anemia, large granular lymphocyte leukemia)
* Congenital syndromes (eg, Fanconi anemia, X-linked sideroblastic anemia)
* Idiopathic cytopenia of undetermined significance (ICUS)
* Idiopathic dysplasia of undetermined significance (IDUS)

## 

## **Differential Diagnoses**

* Anemia
* Aplastic Anemia
* Bone Marrow Failure
* Chronic Myelogenous Leukemia (CML)
* Felty Syndrome
* Hairy Cell Leukemia
* Idiopathic Cytopenia of Undetermined Significance (ICUS)
* Idiopathic Dysplasia of Undetermined Significance (IDUS)
* Immune Thrombocytopenia (ITP) in Emergency Medicine
* Megaloblastic Anemia
* Myelophthisic Anemia
* Myeloproliferative Disease
* Neutropenia
* Platelet Disorders

## **Outlook / Prognosis**

The only cure for MDS is a successful stem cell transplant. Unfortunately, not everyone can have this treatment. Ask your healthcare provider if a transplant is a choice you should consider.

### **What is the life expectancy for someone with myelodysplastic syndrome?**

Myelodysplastic syndrome is a serious health issue that can cause life-threatening conditions. It’s also a complicated health issue that affects people in different ways. Your healthcare provider is your best source of information about your individual prognosis or expected outcome.

## **Prevention**

No, but understanding MDS risk factors may help healthcare providers diagnose and treat MDS early on. Myelodysplasia syndrome is linked to chemotherapy and radiation therapy, as well as exposure to certain chemicals and heavy metals. Talk to your healthcare provider about your medical history and any activities that placed you in close and prolonged contact with chemicals and heavy metals. They’ll help you assess your personal risk.

## **Living With**

MDS affects people in different ways. Some people have MDS but no symptoms. If that’s your situation, your provider may recommend blood tests every three months to monitor any changes in your blood stem cells. If you have MDS and are receiving supportive treatment such as blood transfusions, you may need more treatment to reduce how many blood transfusions you need. Here are some steps you can take that may support your treatment:

* If you use tobacco products (including vaping), try to stop. Ask your healthcare provider about tobacco cessation programs.
* Reach and maintain a weight that’s healthy for you.
* Find physical activities that you enjoy and participate in them as often as you can.
* Remember that MDS is a chronic illness that healthcare providers can treat but they can’t cure. Not everyone will understand what you’re going through. It may help to talk to others who share your experience. Your healthcare team may be able to help you find programs and resources.

Myelodysplastic syndrome can cause conditions like anemia, bleeding issues and infections. You should go to the emergency room any time you:

* Develop a fever that’s 100.4 degrees Fahrenheit (38.3 degrees Celsius) or higher. A fever may be a sign you have an infection.
* You have bleeding that you can’t control.

### **What questions should I ask my healthcare provider?**

Myelodysplastic syndrome is rare, so you’ll likely have many questions about what you can expect. Here are some questions you may want to ask your healthcare provider:

* Is MDS cancer?
* How am I affected by MDS?
* Will my MDS cause serious health problems, and if so, what kind?
* I don’t have symptoms. What can I do to delay conditions related to MDS?

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**GRAY ZONE LYMPHOMA**

**DEFINITION AND DESCRIPTION**

Gray zone lymphoma is an aggressive and rare type of lymphoma. Because it’s rare, diagnosis and treatment can be difficult. However, people in the early stages respond well to chemotherapy, radiation, and stem cell transplants.

Gray zone lymphoma is a rare type of lymphoma that shares characteristics of both Hodgkin’s lymphoma and a type of non-Hodgkin’s lymphoma called primary mediastinal B-cell lymphoma (PMBCL).

Some people are treated for Hodgkin’s lymphoma and PMBCL unsuccessfully before they’re diagnosed with gray zone lymphoma. This confusion is what earned gray zone lymphoma its name when it was first recognized as a distinct type of lymphoma in 2008.

## **symptoms of gray zone lymphoma**

Gray zone lymphoma causes swelling in your thymus, a small gland under your breastbone, and in the nearby lymph nodes. As the tumor grows and swelling increases, many people with gray zone lymphoma notice a lump in their chest, near their breast bone.

Sometimes, this swelling is painful or results in pressure in the chest. The tumor growth can also press on the lungs and throat, leading to difficulty eating, talking, and breathing.

Gray zone lymphoma also causes generalized lymphoma symptoms. These include:

* swollen lymph nodes in the neck, groin, or under the arms
* loss of appetite
* unintentional weight loss
* itchy skin
* easy bruising
* excessive bleeding from minor cuts, nosebleeds, or other small injuries
* bleeding gums
* heavy menstrual periods
* fatigue
* night sweats
* high fever

## **causes and risk factor**

Gray zone lymphoma is rare, and there’s no known cause for this cancer. Experts believe that infection with the Epstein-Barr virus can increase the risk of gray zone lymphoma. However, the virus doesn’t directly cause cancer, and people who’ve never had Epstein-Barr can develop gray zone lymphoma.

Research also shows that, while gray zone lymphoma can occur in people of any age or gender, it’s more common in people who are between 20 and 40 years old and in people assigned male at birth.

You’re also more at risk for gray zone lymphoma if you have any risk factors for all types of lymphoma:

* having a family member with lymphoma
* having a family member with chronic leukemia
* having a condition that weakens your immune system
* having an autoimmune condition
* taking a medication that weakens your immune system
* having prolonged workplace exposure to pesticides, herbicides, fungicides, solvents, paints, oil, fuel, infectious organisms, dust, or hair dye.
* having any type of cancer in the past

## **How is gray zone lymphoma diagnosed and staged?**

The first step to getting diagnosed with gray zone lymphoma is a medical appointment. At your appointment, your doctor will ask you about your symptoms and your medical history. If they suspect you might have any type of lymphoma, they’ll order tests to help confirm the diagnosis.

Common tests for gray zone lymphoma include:

* Blood tests: Blood tests will look at the numbers of red blood cells, white blood cells, and platelets in your blood. Lymphoma can affect how many of these cells are circulating in your blood.
* Biopsies: Biopsies will be done on any swollen lymph nodes or glands. Biopsies remove samples of the affected node or gland so that it can be tested for cancer in a lab. Typically, biopsies for gray zone lymphoma are done by inserting a thin and hollow needle into the node or gland.

Biopsies are typically the best way to confirm cancer. Once you’ve been diagnosed with gray zone lymphoma, you’ll have additional tests to stage your cancer.

Staging is a system that addresses how far cancer has progressed. It helps doctors plan your treatment and helps you get a better understanding of your outlook. Gray zone lymphoma staging is based on:

* how many areas of your body have lymphoma
* which parts of your body have lymphoma
* whether the lymphoma has spread to your bone marrow
* whether the lymphoma has spread to organs, including the liver, skin, and lungs

### **Staging of gray zone lymphoma**

There are four stages of gray zone lymphoma. In stages 1 and 2, the cancer is early stage and hasn’t yet spread throughout the body. In stages 3 and 4, cancer is advanced and has spread throughout the body, including to organs and bone marrow. The exact breakdown of stages is:

* Stage 1: Cancer is contained to one lymph node.
* Stage 2: Cancer is contained to two or more lymph nodes on the same side of the diaphragm
* Stage 3: Cancer is in at least one lymph node above the diaphragm and one lymph node below the diaphragm.
* Stage 4: Cancer has spread throughout the body and to distant organs.

## **Treatment**

Gray zone lymphoma is rare, and there’s no standard treatment. Your doctor will look at your test results and develop the treatment plan that is best for you.

Common gray zone lymphoma treatments include:

* chemotherapy
* radiation therapy
* stem cell transplants

**outlook for gray zone lymphoma?**

Gray zone lymphoma is a rare and unique type of lymphoma that has only recently been recognized. This makes it difficult to obtain the kind of survival statistics that have been gathered for other cancers and conditions.

A 2020 study looked at accumulated data on patients with gray zone lymphoma across the United States. They found that people with gray zone lymphoma had a 68% chance of survival in the 3 years following their diagnosis.

The study also found that age at diagnosis and stage of cancer at diagnosis had a large impact on survival. Younger people who were treated in earlier stages saw much better outcomes.

## **differential diagnosis:**

1. Classical Hodgkin Lymphoma (cHL), especially Nodular Sclerosis subtype (NSCHL)
   * Shares morphological features such as Reed-Sternberg (HRS) cells and fibrosis.
   * cHL typically shows strong CD30 and CD15 expression, weak or absent B-cell markers (CD20, CD79a), and downregulated PAX5.
   * GZL shows overlap with cHL but often has stronger or more variable B-cell marker expression.
2. Primary Mediastinal Large B-Cell Lymphoma (PMBL)
   * A subtype of DLBCL arising in the mediastinum with characteristic gene expression and immunophenotype.
   * PMBL expresses B-cell markers strongly (CD20, CD79a, PAX5), often CD23, and lacks CD15.
   * GZL shows intermediate immunophenotype with partial expression of these markers.
3. Diffuse Large B-Cell Lymphoma (DLBCL), not otherwise specified
   * Shares large cell morphology but usually lacks the classical Hodgkin features.
   * Immunophenotype is fully B-cell lineage positive.
4. EBV-positive lymphomas (EBV+ cHL and EBV+ DLBCL)
   * Rare EBV-associated cases may mimic GZL and require EBV-encoded RNA (EBER) testing for distinction.
5. Other mediastinal lymphomas
   * Includes T-cell lymphomas or other rare entities, but these are less common in the differential.

**EPIDEMIOLOGY**

* Incidence:
  + The estimated incidence rate for GZL is approximately 0.53 per million person-years based on confirmed cases in the United States between 2005 and 2016 .
  + The incidence of GZL has shown an increase over time, rising from 0.14 in 2005 to 1.27 in 2016 .
* Age:
  + GZL primarily affects young adults, with a median age at diagnosis typically ranging from 32 to 37 years .
  + Only a small proportion of patients (around 16-22%) are older than 60 years at diagnosis .
* Sex:
  + There is a consistent male predominance in GZL. The male-to-female ratio is about 1.4:1 for mediastinal GZL and has been reported as high as 1.9:1 in consensus-confirmed cases . This contrasts with PMBL and classical Hodgkin lymphoma, which tend to have a female predominance .
* Location:
  + Mediastinal involvement is a common presentation, observed in nearly 70% of consensus-confirmed GZL cases . Mediastinal Gray Zone Lymphoma (MGZL) is specifically defined as having morphologic and phenotypic features similar to both classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma, and it is found in the mediastinum .
  + Cases presenting outside the mediastinum without mediastinal involvement are now generally classified as Diffuse Large B-cell Lymphoma, not otherwise specified (DLBCL, NOS), and are no longer considered a subset of GZL as of 2022 .
* Rarity and Diagnostic Challenges:
  + Due to its rarity and complex features, GZL is a diagnostic dilemma for pathologists and oncologists .
  + A study involving 68 cases initially diagnosed as GZL across 15 North American academic centers found that after central pathology review, only 26 (38%) were ultimately confirmed as GZL, highlighting the difficulty in accurate diagnosis .
* Survival:
  + The 5-year overall survival (OS) rates for treated GZL patients have been reported at approximately 75.1% .
  + Another study indicated a 68% chance of survival within 3 years following diagnosis

REFERENCES

[Gray Zone Lymphoma - DoveMed](https://www.dovemed.com/diseases-conditions/gray-zone-lymphoma)

**MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE(MGUS)**

Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which an atypical protein is found in the blood. The protein is called monoclonal protein or M protein.

This protein is made in the soft, blood-producing tissue in the center of bones. This blood-producing tissue is bone marrow. Monoclonal gammopathy of undetermined significance occurs most often in older men.

MGUS usually causes no problems. But sometimes it can lead to more-serious diseases. These include some forms of blood cancer.

People who have high amounts of this protein in the blood need regular checkups. That's so they can get earlier treatment if the condition gets worse. If it doesn't get worse, MGUS doesn't need treatment.

**Causes**

Experts don't know what causes MGUS. Changes in genes and being around certain chemicals, such as those used to kill pests, appear to play a role.

**Risk factors**

Factors that increase your risk of developing MGUS include:

* **Age.** The average age at diagnosis is 70 years.
* **Race.** Africans and Black Americans are more likely to get MGUS than white people are.
* **Sex.** MGUS is more common in men.
* **Family history.** Having family members with MGUS might increase the risk.

**Complications**

Each year, about 1% of people with MGUS get certain types of blood cancers or other serious diseases, such as:

* Multiple myeloma.
* Light chain amyloidosis.
* Waldenstrom macroglobulinemia.
* Lymphoma.

Other issues linked to MGUS include broken bones, blood clots, kidney problems, and damage to nerves outside of the brain and spinal cord, also known as peripheral neuropathy.

## **Diagnosis**

Because MGUS usually causes no symptoms, people who have it usually find out by chance during blood tests for other reasons. After that, other tests might include:

* **More blood tests.** These can help rule out other causes of higher protein levels. And they can check for kidney damage.
* **Urine tests.** Urine samples taken over 24 hours can help find if the atypical protein is in the urine. They also can check for kidney damage.
* **Imaging tests.** For people with bone pain, an, MRI or positron emission tomography (PET) scan can look for problems with bones from MGUS. They also might need a test to measure bone mass, also known as bone density.
* **Bone marrow test.** A hollow needle removes a piece of bone marrow from the back of one of the hipbones for study. This usually is only for those at risk of getting a more serious disease or other problems linked to MGUS.

**Treatment**

MGUS doesn't require treatment. But your health care provider is likely to have you get regular checkups to watch the condition. Checkups likely will start six months after your diagnosis.

### **Watchful waiting**

For those at high risk of MGUS leading to a more serious condition, more-frequent checkups can watch the disease. That way, treatment can start as soon as possible if it's needed.

Symptoms to watch for include:

* Bone pain.
* Tiredness or weakness.
* Weight loss without trying.
* Fever or night sweats.
* Headache, dizziness, nerve pain, or changes in vision or hearing.
* Bleeding.
* Anemia or other blood irregularities.
* Swollen lymph nodes, liver or spleen.

### **Medicines**

Medicine for the bone-thinning disease known as osteoporosis increase bone mass. Examples include alendronate (Fosamax), risedronate (Actonel, Atelvia), ibandronate and zoledronic acid (Reclast, Zometa).

## **Outlook / Prognosis**

In general, most people with MGUS don’t have symptoms. Many never need treatment. A small percentage of people develop certain blood cancers or blood disorders that do require treatment with pills or other medications.

If blood and urine tests show M proteins, you’ll need regular blood and urine tests at least every six to 12 months. That way, your healthcare providers can watch for signs that MGUS is becoming a serious condition.

It’s unclear how MGUS impacts a person’s life expectancy. But screenings after a MGUS diagnosis improve survival rates for people who develop multiple myeloma.

## **Diagnostic Considerations**

Monoclonal gammopathy of undetermined significance (MGUS) must be differentiated from overt malignant diseases, such as the following:​​

* Multiple myeloma (MM)
* Immunoglobulin light-chain (AL) amyloidosis
* Monoclonal gammopathy of clinical significance (MGCS)
* Myoclonal gammopathy of renal significance (MGRS)

Criteria for MGUS established by the International Myeloma Working Groupand the World Health Organizationare as follows:

* Serum M-protein level < 3 g/dL
* Bone marrow plasma cells < 10% and low level of plasma cell infiltration in a trephine biopsy specimen
* No evidence of B-cell proliferative disorder (ie, MM, Waldenström macroglobulinemia, AL amyloidosis)
* No M-protein or only small amounts of monoclonal light chain in urine
* No osteolytic lesions, anemia, hypercalcemia, or M-protein–related kidney function impairment

In addition to the hematologic abnormalities, MGRS is associated with a wide spectrum of kidney diseases, including AL amyloidosis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, and C3 glomerulopathy with monoclonal gammopathy. Kidney biopsy is indicated in most cases of MGRS, to identify the exact lesion and determine its severity.Treatment to eradicate the underlying clone is indicated; the proteasome inhibitor bortezomib is the preferred therapy in MGRS but a number of other agents have been used in some settings, including rituximab, cytotoxic chemotherapy, and immunomodulatory agents.

Asymptomatic patients who have an M-component higher than 3 g/dL, or more than 10% but less than 20% bone marrow plasma cells, fulfill the criteria for smoldering multiple myeloma (SMM). These patients do not have anemia, kidney failure, hypercalcemia, osteolytic bone lesions, or other clinical manifestations related to the monoclonal protein.

Serum M-component (IgG or IgA) > 3 g/dL or urinary M-component > 500 mg/24 hours and clonal BMPC ≥10% and <60%Absence of myeloma-defining events, such as end-organ damage (CRAB), or other biomarkers of malignancy (SLiM)\*,or amyloidosis, that can be attributed to the plasma cell proliferative disorder

In clinical and biologic terms, SMM is closer to MGUS than to overt MM. Traditionally, patients with SMM have not been treated with chemotherapy until progression occurs; in recent years, however, risk stratification models for SMM have been developed, and studies have reported that treatment of patients with high-risk SMM can significantly slow progression to MM. No particular laboratory parameter or clinical factor differentiates MGUS or SMM from overt MM. Decreased levels of uninvolved immunoglobulins are not a useful criterion for differentiation because 30-40% of patients with MGUS also have decreased levels of the uninvolved immunoglobulins.

Although Bence-Jones proteinuria suggests MM, finding small amounts of monoclonal light chains in the urine of patients with MGUS is not unusual. Lytic bone lesions on the skeletal survey strongly suggest MM. In patients recently diagnosed with MGUS, serum electrophoresis should be repeated after 3 months to exclude early myeloma, and, if the results are stable, the test should be repeated in 6 months. Patients should be aware that the evolution of MGUS to MM can be abrupt; therefore, they should be reexamined promptly if their clinical condition deteriorates.

## **Differential Diagnoses**

* Amyloidosis
* Multiple Myeloma
* Non-Hodgkin Lymphoma (NHL)
* Waldenstrom Macroglobulinemia

## **Epidemiology**

MGUS represents two thirds of all plasma cell dyscrasias. The incidence increases with age. In a study of residents of Olmsted County, Minnesota, MGUS was found in 3.2% of persons 50 years of age or older, 5.3% of those 70 years of age or older, and 7.5% of those 85 years of age or older. Subsequently, however, Murray et al used mass spectrometry to retest the baseline samples in 300 of the Olmsted County residents who had a negative work-up for monoclonal proteins but later developed MGUS. This more sensitive assay revealed a prevalence of MGUS of 5.1% among persons 50 years of age and older.

In a study of 154,597 persons in Beijing, China who underwent annual medical checkups, median age at presentation with MGUS was 58 years (range, 25–96). The prevalence of MGUS increased with increasing age: the overall prevalence was 1.11% among participants aged ≥50 years, 2.57% among those aged ≥70 years, and 3.77% in those ≥80 years.

The prevalence of MGUS is higher in HIV-infected patients, although it decreased with the adoption of antiretroviral therapy. In a study of 383 French HIV-infected patients, 359 of whom were on antiretroviral therapy for a median duration of 105 months, there were 12 (3.1%) cases of MGUS, including five IgG kappa cases, 5 IgG lambda cases, one biclonal (2 IgG kappa) case, and one case with three monoclonal immunoglobulins (IgG kappa×2+IgG lambda). In all cases, the monoclonal immunoglobulin levels were low, and the level was below 1 g/L in all cases except two. No factors were found to be predictive of MGUS.

In a prospective cohort study in Vietnam war veterans, the crude prevalence of overall MGUS was 7.1% (34 of 479) in veterans involved in the spraying of Agent Orange, versus 3.1% (15 of 479) in veterans who were not involved in herbicide spray missions. After adjustment for factors including age, race, and body mass index, this translated into a 2.4-fold increased risk for MGUS in exposed veterans (adjusted odds ratio, 2.37; 95% CI, 1.27-4.44; P = 0.007).

In a study of firefighters involved in rescue and/or recovery work at the New York World Trade Center after the September 11, 2001 attack, Landdgren et al reported an age-standardized prevalence rate of MGUS and light-chain MGUS combined of 7.63 per 100 persons (95% CI, 5.45-9.81), which is 1.8-fold higher than rates from a reference population; the rate of light-chain MGUS was more than 3-fold higher than in the same reference population. Of the 781 firefighters studied, 16 had been diagnosed with multiple myeloma (7 of them with light-chain disease), at a median age of 57 years.

### Mortality/Morbidity

Patients with MGUS tend to do well when treated conservatively.Regular surveillance is required to assess for progression to either a lymphoproliferative disorder or to MM.This risk has been quantified at 1% per year.

### Race-, Sex-, and Age-related Variances

A retrospective study by the US Department of Veterans Affairs revealed that the age-adjusted prevalence ratio of MGUS in black patients was 3.0 compared with white patients.For a discussion of possible genetic factors in the pathogenesis of MGUS, see Landgren et al.

MGUS occurs more commonly in men than in women, and the prognosis for men was worse than that of women in some studies.

Age-related differences in incidence are as follows:

* The median age of patients with the disease is 70 years; however, most physicians are observing patients younger than this, possibly because of improved screening rather than an increased incidence of the process.
* The incidence of MGUS is higher in older patients than in younger patients; of patients older than 80 years, the available literature suggests as many as 10-15% may have an M-protein.

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