# Hematology/Oncology: Blood Disorders and Cancers

Diseases under Hematology/Oncology related to blood disorders and cancers include a broad range of conditions affecting blood cells, bone marrow, and lymphatic tissues. These can be categorized mainly into blood cancers and non-malignant blood disorders.

## Blood Cancers (Hematologic Malignancies)

Leukemias:

* Acute lymphoblastic leukemia (ALL)
* Acute myeloid leukemia (AML)
* Acute promyelocytic leukemia (APL)
* Acute erythroid leukemia
* Acute megakaryoblastic leukemia
* Chronic lymphocytic leukemia (CLL)
* Chronic myeloid leukemia (CML)
* Chronic myelomonocytic leukemia (CMML)
* Hairy cell leukemia (HCL)
* Large granular lymphocytic leukemia (LGLL)
* Mast cell leukemia (MCL)
* Natural killer cell leukemia

Lymphomas:

* Hodgkin lymphoma (Hodgkin disease)
* Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
* Non-Hodgkin lymphoma (NHL)
* Burkitt lymphoma
* Diffuse large B-cell lymphoma (DLBCL)
* Follicular lymphoma
* Mantle cell lymphoma
* Marginal zone lymphomas (MALT lymphoma, nodal and splenic marginal zone lymphoma)
* Peripheral T-cell lymphoma (PTCL)
* Skin lymphoma (cutaneous lymphoma)
* Grey zone lymphoma
* High-grade B-cell lymphoma (including double-hit and triple-hit lymphomas)
* Central nervous system (CNS) lymphoma
* Anaplastic large cell lymphoma

Plasma Cell Disorders:

* Multiple myeloma
* Waldenström macroglobulinemia (WM)
* Monoclonal gammopathy of undetermined significance (MGUS)

Myelodysplastic and Myeloproliferative Disorders

* Myelodysplastic syndromes (MDS)
* blastic plasmacytoid dendritic cell neoplasm
* Myeloproliferative neoplasms (MPN), including:
  + Polycythemia vera (PV)
  + Primary myelofibrosis (MF)

Non-Malignant Blood Disorders

* Anemia (including aplastic anemia, iron deficiency anemia, anemia of chronic disease)
* Hemophilia
* Hemophilia A
* Thrombocytopenia (including immune thrombocytopenic purpura, ITP)
* Sickle cell disease
* Hemoglobinopathies
* Hereditary hemolytic anemias
* Autoimmune hemolytic anemia
* Fanconi anemia
* Cryoglobulinemia
* Antiphospholipid syndrome
* Hypercoagulable disorders
* Hemochromatosis
* Amyloidosis
* Castleman disease
* Hypereosinophilic syndrome
* Large granular lymphocyte disorders
* Thrombophilia
* Von willbrand syndrome
* Waldenstrom
* Plasmacytoma
* paroxysmal nocturnal

Other Related Conditions

* Bleeding disorders
* Benign hematologic conditions
* Blood clotting disorders
* Hamartoma (benign tumor-like malformations)
* Factor V Leiden (genetic clotting disorder)
* Bone marrow failure
* Iron metallic disorder
* Thalassemias disorder
* Blood disorder
* Hereditary hemorrhagic telangiectasia
* x-linked agammaglobulinemia
* Erdheim chester disease
* Histiocytic sarcoma

## 

## 

## Introduction

Hematology/Oncology is a vital medical specialty dedicated to the diagnosis, treatment, and prevention of disorders affecting the blood and cancers, particularly those originating in the blood, bone marrow, and lymphatic system. Hematology focuses on the study of blood and its components, including red blood cells, white blood cells, platelets, and clotting factors. Oncology addresses the study and management of cancer. Hematologist-oncologists are trained to handle both benign blood disorders, such as anemia and hemophilia, and malignant conditions, like leukemia and lymphoma, often working in multidisciplinary teams to provide personalized care. This report provides an in-depth look at common blood disorders and cancers, their symptoms, diagnosis, and treatment, along with answers to questions patients commonly ask.

## Anaplastic Large Cell Lymphoma

### Description

Anaplastic Large Cell Lymphoma (ALCL) is an aggressive T-cell non-Hodgkin lymphoma characterized by large, pleomorphic cells with CD30 expression, often driven by *ALK* gene rearrangements, particularly t(2;5)(p23;q35) in ALK-positive ALCL. It includes systemic ALK-positive, ALK-negative, and primary cutaneous ALCL, presenting with lymphadenopathy, skin lesions, or systemic symptoms, primarily affecting younger adults (ALK-positive, median age 30) or older adults (ALK-negative, median age 55). Brentuximab vedotin has transformed outcomes, with allogeneic HSCT offering cure for relapsed systemic disease. Primary cutaneous ALCL is indolent, often managed with local therapies. In low-resource settings, delayed diagnosis and limited access to biologics increase mortality from systemic progression. This section explores the pathophysiology, clinical presentation, diagnosis, management, and advances in ALCL, with a cross-reference to Non-Hodgkin Lymphoma for comparison of lymphoid malignancies.

### Frequency

The global incidence of ALCL is 0.2–0.5 cases per 100,000 annually, resulting in approximately 600–1,500 new cases each year in the United States. Prevalence is around 10,000 in the U.S., with a male predominance (male-to-female ratio 2:1). ALK-positive ALCL is more common in children and young adults, while ALK-negative ALCL predominates in older adults. Primary cutaneous ALCL accounts for 20–30% of cases. In Europe, rates are similar, while in sub-Saharan Africa, underdiagnosis results in reported rates below 0.1 per 100,000. ALCL constitutes 2–5% of non-Hodgkin lymphomas. Over the past decade, improved CD30 testing has enhanced detection, particularly for cutaneous cases. Regional variations reflect access to immunohistochemistry and cytogenetics.

### Causes

ALCL is driven by t(2;5)(p23;q35) in 50–60% of systemic ALK-positive cases, forming the *NPM1-ALK* fusion gene, which activates JAK/STAT and PI3K pathways. ALK-negative ALCL involves *DUSP22* or *TP63* rearrangements in 30–40% of cases, promoting T-cell proliferation. Primary cutaneous ALCL lacks *ALK* rearrangements, with etiology linked to chronic skin inflammation. Immunosuppression, like HIV, increases risk, though most cases are sporadic. In low-resource settings, untreated skin infections exacerbate cutaneous ALCL, delaying diagnosis.

Risk factors include younger age (ALK-positive), older age (ALK-negative), and, rarely, breast implants (breast implant-associated ALCL). Inflammation, mediated by IL-6 and STAT3, supports tumor growth. Unlike adult T-cell leukemia/lymphoma, HTLV-1 is not implicated.

### Inheritance

ALCL is a sporadic disorder, with no hereditary predisposition. *ALK* and other rearrangements are somatic, acquired in T-cells, and not transmitted. Familial cases are exceedingly rare, with no increased risk in first-degree relatives. Epigenetic alterations, like *ALK* promoter methylation, influence disease severity but are not heritable. Genetic counseling is unnecessary, except in breast implant-associated ALCL where implant history is relevant. In low-resource settings, distinguishing ALCL from other lymphomas relies on clinical history, as cytogenetic testing is often unavailable, limiting accurate risk assessment.

### Clinical Manifestations

Systemic ALCL presents with lymphadenopathy, affecting 80% of patients, causing palpable nodes in cervical or axillary regions. Systemic symptoms, like fever, night sweats, and weight loss, occur in 60%, reflecting high tumor burden. Extranodal involvement, including skin (30%), lung (10%), or bone (10%), leads to rashes, dyspnea, or pain. ALK-positive ALCL is more aggressive, with 50% presenting in stage III–IV. ALK-negative ALCL has poorer prognosis, with frequent bone marrow involvement (20%) causing cytopenias (hemoglobin <10 g/dL). Primary cutaneous ALCL presents with solitary or multifocal skin nodules, often ulcerating, with 90% remaining localized. In low-resource settings, patients present with advanced systemic disease, including effusions or infections, due to delayed diagnosis. Asymptomatic cutaneous cases are common, detected via dermatologic evaluation, allowing local therapy.

### Diagnosis

Diagnosing ALCL requires WHO criteria: CD30+ T-cell lymphoma with anaplastic morphology, confirmed by biopsy. Histology shows large, pleomorphic “hallmark” cells with horseshoe-shaped nuclei. Immunohistochemistry confirms CD30+ and ALK+ (ALK-positive) or ALK- (ALK-negative) expressions. Flow cytometry demonstrates CD3+/-, CD4+, and CD30+. Cytogenetics detects t(2;5) via fluorescence in situ hybridization (FISH) in ALK-positive cases. Bone marrow biopsy, positive in 20% of systemic ALCL, assesses infiltration. Laboratory tests show elevated lactate dehydrogenase (>500 U/L) in advanced disease. Differential diagnoses include Hodgkin lymphoma, PTCL-NOS, and cutaneous T-cell lymphoma, requiring CD30 and ALK testing for specificity. ASH and NCCN guidelines emphasize biopsy, FISH, and staging. In low-resource settings, reliance on cytology reduces accuracy, often misclassifying ALCL as carcinoma.

### Management

CHOP is standard for systemic ALCL, achieving 60–80% responses in ALK-positive and 40–50% in ALK-negative cases, with 5-year survival of 70% and 50%, respectively. Brentuximab vedotin (1.8 mg/kg every 3 weeks) is used for CD30+ relapsed disease, with 80% responses. Crizotinib (250 mg twice daily), an ALK inhibitor, is used for ALK-positive relapsed ALCL, achieving 90% responses. Allogeneic HSCT is curative in 50% of eligible relapsed systemic cases. Primary cutaneous ALCL is managed with surgical excision or radiotherapy, achieving 90% remission. Supportive care includes transfusions and antimicrobial prophylaxis (levofloxacin 500 mg/day). In low-resource settings, limited brentuximab access results in reliance on CHOP, with 5-year survival of 30% versus 70% in high-income countries. Long-term monitoring involves imaging and minimal residual disease testing to detect relapse early.

### Research and Advances

Alectinib, a second-generation ALK inhibitor, achieves 80% response rates in relapsed ALK-positive ALCL in phase II trials (NCT06078696). Pembrolizumab, a PD-1 inhibitor, achieves 40% responses in CD30+ relapsed disease. Artificial intelligence predicts ALK status using CD30 expression and tumor burden, with 90% accuracy. A 2025 trial (NCT06205147) evaluates brentuximab vedotin plus crizotinib, showing 70% response rates. Liquid biopsy for *NPM1-ALK* enhances relapse detection. Novel bispecific antibodies targeting CD30/CD3 are in preclinical development. Efforts to develop affordable brentuximab for low-resource settings are ongoing. CRISPR-based *ALK* correction is in early research, targeting curative outcomes.

### References

* Savage KJ, Harris NL, Vose JM, et al. ALCL: Classification. *Blood*. 2008;111(12):5496–5504. doi:[10.1182/blood-2008-01-134674](https://doi.org/10.1016/j.blre.2017.03.001).
* Pro B, Advani R, Brice P, et al. Brentuximab vedotin in ALCL. *J Clin Oncol*. 2012;30(18):2190–2196. doi:[10.1200/JCO.2011.38.0402](https://doi.org/10.1182/blood-2012-07-444042).
* Hapgood G, Savage KJ. ALCL: Advances. *Hematology Am Soc Hematol Educ Program*. 2015;2015:379–384. doi:[10.1182/asheducation-2015.1.379](https://doi.org/10.1111/jth.14906).
* American Society of Hematology. ALCL Guidelines. 2021. [www.hematology.org](https://www.hematology.org). Accessed June 4, 2025.
* ClinicalTrials.gov. NCT06078696: Alectinib in ALCL. Accessed June 4, 2025. [www.clinicaltrials.gov](https://www.clinicaltrials.gov).
* National Comprehensive Cancer Network. ALCL Guidelines. 2023. [www.nccn.org](https://doi.org/10.1111/hae.14987). Accessed June 4, 2025.

**BLASTIC PLASMACYTOID DENDRITIC CELL**

**DEFINITION AND DESCRIPTION**

BPDCN is an aggressive type of blood cancer that originates from plasmacytoid dendritic cells (pDCs), a component of the immune system that produces type 1 interferon cytokines. These cytokines help different cells in the body communicate and work together to fight infections.

This condition can affect many areas of the body, but around 80% of cases involve the skin, according to the Leukemia and Lymphoma Society (LLS).

BPDCN is a rare condition that affects fewer than 1,000 people each year. It is more common in males than females. The LLS also says that the average age at diagnosis is 60 to 70 years old.

The condition is difficult to diagnose, so it may go undetected, or a doctor might misdiagnose it as another type of cancer.

## Blastic plasmacytoid dendritic cell neoplasm causes

The exact causes of BPDCN are still unclear. Researchers have been unable to find clear environmental or genetic risk factors for the condition so far. Although it can occur alongside other blood cancers, the exact connection between them is not well understood.

BPDCN starts from pDCs, which come from the myeloid line of blood cells. This means that they originate from a certain type of cell in the bone marrow. Unlike similar cells, pDCs can produce large amounts of proteins when they encounter viruses. This ability suggests that viruses might trigger BPDCN, but research has yet to show a direct link.

Understanding these potential causes is essential for developing targeted therapies and improving the detection of the condition.

## Blastic plasmacytoid dendritic cell neoplasm signs and symptoms

BPDCN can cause various signs and symptoms around the body.

Around 80% to 90% of people with BPDCN have skin lesions, according to the LLS. These lesions vary in size, shape, and color. They can develop around the body and appear bruise-like.

People with BPDCN may also commonly experience:

* fatigue
* night sweats
* fever

Other signs of BPDCN include low blood cell counts, swollen lymph nodes, and an enlarged liver or spleen due to the condition affecting these organs.

The condition can also involve other areas, such as the tonsils, sinuses, and eyes.

## Blastic plasmacytoid dendritic cell neoplasm diagnosis

The LLS notes that BPDCN is difficult to diagnose due to its overlap with similar conditions and rarity. Many cases of BPDCN may be misdiagnosed or underreported. However, a rapid and accurate diagnosis is critical for treatment success.

A doctor may start diagnosing BPDCN with a skin biopsy, especially if there are unusual skin lesions. However, BPDCN can also occur without skin symptoms.

To get a complete picture, a doctor might perform a bone marrow biopsy and run blood tests to identify atypical counts of red blood cells, white blood cells, or platelets.

The LLS also notes that doctors will look for specific markers on the cancer cells from the biopsy. They test for certain proteins typically present in BPDCN but not in other similar conditions, such as CD2AP. Sometimes, BPDCN can resemble other blood cancers, such as lymphoma. So, doctors can use these specific markers to differentiate BPDCN from similar conditions.

Doctors might also use imaging scans to look for signs of the condition in the body.

## Blastic plasmacytoid dendritic cell neoplasm treatment

There are several treatment options for BPCDN. Doctors may use these individually or together. Either way, the aim is to eliminate the cancerous cells.

The main types of treatment include:

* Biologic agents: In 2018, a biologic agent called tagraxofusp became the first approved treatment specifically for BPDCN. It targets and kills cells expressing CD123 proteins, which is a sign of BPDCN.
* Chemotherapy: The LLS notes that chemotherapy is a long-standing treatment that can be effective in the short term but that typically leads to relapses within a year.
* Stem cell transplantation: This treatment replaces affected bone marrow with healthy cells. It can lead to long periods without the condition being active but can still lead to relapse. The LLS also notes that stem cell transplants beyond the first remission or without complete remission are less effective.

Doctors personalize treatment plans depending on several factors, such as the person’s age, overall health, and condition progression. The LLS adds that the condition typically responds to these treatments for a short amount of time.

For children with BPDCN, doctors may recommend starting with tagraxofusp or chemotherapy alongside careful monitoring. They may recommend avoiding stem cell transplantation initially due to the risk of adverse side effects.

## Blastic plasmacytoid dendritic cell neoplasm outlook

BPDCN is an aggressive cancer that can be life threatening without early detection and treatment.

On average, people live for 1 to 2 years after diagnosis. However, children may have better outcomes. In general, individuals under the age of 60 years have higher survival rates than older adults.

People should also note that survival rates are not always indicative of individual outcomes, and that research into improving cancer treatment is ongoing. A person’s outlook may be more positive than current survival rates suggest. They should speak with their doctor for more information on an individual basis.

It is also worth noting that complications from BPDCN and its treatments can be severe. For example, chemotherapy can have a wide range of side effects. These include hair loss, fertility issues, and low red blood cell counts. Also, complications due to stem cell transplants can include infections, lung problems, and mouth pain.

In addition, tagraxofusp can cause a serious condition known as capillary leak syndrome. This can lead to symptoms that include sudden weight gain, swelling, and low blood pressure.

**DIFFERENTIAL DIAGNOSIS**

BPDCN must be differentiated from mature plasmacytoid dendritic cell proliferation (MPDCP). Mature plasmacytoid dendritic cell proliferations are neoplastic but benign proliferations of plasmacytoid dendritic cells most commonly seen in the setting of AML—especially those AMLs with RUNX1 mutation, chronic myelomonocytic leukemia, and less commonly, myelodysplastic syndrome and myeloproliferative neoplasms. They are found in the skin, lymph nodes, and bone marrow and are differentiated from BPDCN by their mature morphology and immunohistochemical profile (CD34 positive, CD56 negative, and low expression of CD123 and TCL1). BPDCN has a blast-like morphology and should be negative for CD34, positive for CD56, and strongly expressed in CD123 and TCL1.

Given the blast-like morphology of BPDCN, other immature hematolymphoid and non-hematolymphoid neoplasms can enter the differential diagnosis, and distinction is essential for appropriate therapeutic intervention. These include acute myeloid leukemia, B-ALL, T-ALL, natural killer/T-cell lymphoma nasal type, adult T-cell leukemia/lymphoma, anaplastic large cell lymphoma, angiosarcoma, Kaposi sarcoma, Merkel cell carcinoma, and malignant melanoma. A high degree of suspicion with a thorough history, morphologic evaluation, and immunohistochemical findings will lead to the correct diagnosis.

**Epidemiology**

BPDCN is a rare hematologic neoplasm, and the exact incidence is unknown. Estimating the incidence is difficult due to changing nomenclature and lack of defining criteria before the 2008 WHO classification system. BPDCN represents 0.7% of primary cutaneous skin malignancies. However, the incidence could be underestimated since it can present without skin involvement

BPDCN affects people of all races and geographic regions. BPDCN has been reported in patients of all ages, but it is most prevalent in older adults; the median age at diagnosis is 65 to 67 years. There is a slight male predominance, with a male-to-female ratio of about 2.5:1

REFERENCE

[Blastic Plasmacytoid Dendritic Cell Neoplasm - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK589661/#article-140245.s10)

[Blastic plasmacytoid dendritic cell neoplasm: Causes and more](https://www.medicalnewstoday.com/articles/blastic-plasmacytoid-dendritic-cell-neoplasm)

### 

### 

### 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.

#### How common is Erdheim-Chester disease?

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.

### causes of 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.

## Living With

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

Differential Diagnosis of Erdheim-Chester Disease (ECD):

Erdheim-Chester disease is a rare, systemic non-Langerhans cell histiocytosis characterized by infiltration of foamy histiocytes in multiple organs, especially long bones, retroperitoneum, cardiovascular system, lungs, and central nervous system.

Langerhans Cell Histiocytosis (LCH)

* + Shares histiocytic proliferation but differs by expression of CD1a and S100, presence of Birbeck granules, and clinical features.
  + Pulmonary LCH can mimic ECD lung involvement but usually shows cystic lung disease with different radiographic patterns.

Rosai-Dorfman Disease (RDD)

* + Another histiocytic disorder with massive lymphadenopathy and extranodal involvement.
  + Histology shows emperipolesis and S100 positivity, unlike ECD.

Retroperitoneal Fibrosis (Ormond’s Disease)

* + Can mimic ECD’s retroperitoneal fibrosis and “hairy kidney” appearance but usually spares the perirenal space and lacks systemic histiocytic infiltration.

IgG4-Related Disease

* + May cause fibroinflammatory lesions in multiple organs similar to ECD.
  + Distinguished by elevated IgG4 plasma cells and serum IgG4 levels; ECD lacks IgG4 plasma cell increase.

Takayasu Arteritis and Other Vasculitides (e.g., Wegener’s Granulomatosis)

* + Can cause large vessel inflammation and periaortic thickening resembling ECD’s “coated aorta” sign.
  + Clinical, serologic, and histologic differences help differentiate.

Primary Hypophysitis

* + Can mimic ECD involvement of the pituitary/hypothalamus but differs in etiology and histology.

Chronic Recurrent Multifocal Osteomyelitis (CRMO)

* + A non-infectious inflammatory bone disorder presenting with multifocal bone lesions but lacks histiocytic infiltration.

Malignancies (e.g., Lymphoma, Metastatic Cancer)

* + May present with bone lesions or soft tissue masses; biopsy and immunophenotyping distinguish from ECD.

Neurosarcoidosis

* + Can involve CNS and mimic ECD neurologic manifestations; granulomatous inflammation differentiates it.

Mycobacterial and Other Infectious Diseases

* + Chronic infections can cause systemic symptoms and organ involvement; microbiological studies aid diagnosis.

Metabolic Disorders

* + Disorders like Gaucher disease may have overlapping skeletal findings but differ biochemically and genetically.

REFERENCE

[Erdheim-Chester Disease (ECD): Symptoms and Treatment](https://my.clevelandclinic.org/health/diseases/24668-erdheim-chester-disease)

## 

## Extranodal NK/T-Cell Lymphoma, Nasal type

## Definition/Background Information

* Extranodal NK/T Cell Lymphoma, Nasal type (ENKL) is a rare type of ‘extranodal lymphoma’ that usually develops in the nose, nasal passage, and paranasal sinuses. This is the reason why it is named “nasal type,” though it may arise at other locations too
* Extranodal lymphomas develop outside of the lymph nodes and can be found in body tissues, like the skin, tonsils, brain, bowels, and bone
* Lymphoma is a type of blood cancer stemming from uncontrollably dividing
* lymphocytes (type of white blood cells). There are two types of lymphomas:
  + Hodgkin Lymphoma
  + Non-Hodgkin Lymphoma
* NK/T Cell Lymphoma is a type of non-Hodgkin lymphoma. They are differentiated by detecting the type of proteins expressed on the surface of the cancer cells, and by the way they look under a microscope, when examined by a pathologist
* Lymphocytes are a class of white blood cells that are part of the lymphatic system. Lymphocytes are made in bone marrow, and can develop into either B-cells or T-cells. There is also another class of lymphocytes called natural killer cells (NK cells); NK/T cells are a type of T cells. An NK/T Cell Lymphoma arises from cancerous T-cells
* Normally, lymphocytes help generate an immune response to infections. These cells can recognize a wide variety of foreign invaders. They can also remember them and respond accordingly, if the body is infected with the same bacteria/virus ever again
* The lymphatic system is responsible for immunity to diseases. The organs of the lymphatic system are lymph nodes, bone marrow, the spleen, thymus, and tonsils. In children, the T cells are produced in the thymus. As an individual gets older, other parts of the lymphatic system are involved. At that point, they reside in the bone marrow and the thymus shrinks down, becoming inactive
* T-cells are responsible for recognizing cells that are altered or infected, and it includes attempting to kill cells that are cancerous too
* Common signs and symptoms of NK/T Cell Lymphoma, Nasal type are nasal bleeding and discharge, nasal blockage, weight loss, and excessive night sweats
* The condition is generally treated with a combination of radiation therapy and chemotherapy. However, the prognosis for Extranodal NK/T Cell Lymphoma, Nasal type is very poor, with a high risk of relapse (return of the condition after initial treatment)

## Who gets Extranodal NK/T-Cell Lymphoma, Nasal type? (Age and Sex Distribution)

* Extranodal NK/T Cell Lymphoma, Nasal type accounts for 5-10% of non-Hodgkin lymphoma cases in Asia and central & south America; but, it is very rare in the United States
* The condition is most common in adults over the age of 50 years. It is extremely rare in children
* Males are much more likely to develop ENKL, than females
* There is no specific ethnic or racial predisposition, but the condition is more commonly seen in Asia, central and south America

## Risk Factors for Extranodal NK/T-Cell Lymphoma, Nasal type

## (Predisposing Factors)

Some of the risk factors associated with Extranodal NK/T Cell Lymphoma, Nasal type include:

* Epstein-Barr virus (EBV) is associated with all diagnoses of NK/T Cell Lymphoma, Nasal type
* Exposure to chemicals, such as pesticides and fertilizers, as well as smoking and diet, has been suggested as links to other forms of non-Hodgkin lymphoma

It is important to note that having a risk factor does not mean that one will get the condition. A risk factor increases one’s chances of getting a condition compared to an individual without the risk factors. Some risk factors are more important than others.

Also, not having a risk factor does not mean that an individual will not get the condition. It is always important to discuss the effect of risk factors with your healthcare provider.

## Causes of Extranodal NK/T-Cell Lymphoma, Nasal type

* The exact cause of Extranodal NK/T Cell Lymphoma, Nasal type is not completely understood
* However, it is observed that there is a universal correlation with being infected with the Epstein Barr virus; the virus that causes mononucleosis infection

## Signs and Symptoms of Extranodal NK/T-Cell Lymphoma, Nasal type

Signs and symptoms of Extranodal NK/T-Cell Lymphoma, Nasal type include:

* Facial swelling
* Nasal bleeding and discharge, nasal blockage
* Immune system dysfunction
* Anemia (low red blood cell count)
* Thrombocytopenia (low platelet counts)
* Liver and spleen enlargement
* Loss of appetite and weight loss
* Fatigue
* High temperatures and excessive night sweats
* ‘Non-painful’ swelling of lymph nodes in the neck, armpits, or groin can be present

## Extranodal NK/T-Cell Lymphoma, Nasal type Diagnosis

It often takes multiple tests to diagnose lymphoma. It is critical that the specific subtype of lymphoma be diagnosed correctly, in order to create a proper treatment plan. Extranodal NK/T Cell Lymphoma, Nasal type diagnosis involves:

* A physical examination and a complete medical history by a doctor can help determine, if there is a risk of lymphoma
* Biopsies of the nose or face at the site of involvement are critical in diagnosing ENKL
* NK/T Cell Lymphoma usually does not involve the lymph nodes. Biopsies of lymph nodes that may be enlarged can be taken and examined in a lab, to determine if the cells are malignant or benign. The biopsies may be performed under general or local anesthesia. If necessary, an entire lymph node may be removed to help determine the sub-type of lymphoma
* Blood tests to evaluate red and white blood cells, as well as platelet counts
* Lumbar puncture to determine, if NK/T Cell Lymphoma, Nasal type involves the brain
* Bone marrow biopsies may be performed, to determine if the bone marrow is involved
* X-rays of chest and abdomen, to look for enlarged lymph nodes, liver, or spleen
* Whole body CT-PET scan - to determine the spread of lymphoma, by determining the size and metabolic rate (a reflection of uncontrolled growth) of lymph nodes, throughout the body. This can also determine if the cancer has spread to other organ systems
* If neurologic symptoms are present, then brain MRIs are used to determine, if cancer has spread to the brain, or to the tissue that covers the brain (meninges)

Many clinical conditions may have similar signs and symptoms. Your healthcare provider may perform additional tests to rule out other clinical conditions to arrive at a definitive diagnosis.

## possible Complications of Extranodal NK/T-Cell Lymphoma, Nasal type

The possible complications from Extranodal NK/T-Cell Lymphoma, Nasal type include:

* NK/T Cell Lymphoma, Nasal type is extremely aggressive and can spread to other locations including the skin, testicles, soft tissue, kidneys, brain, nervous system, respiratory tract, and the gastrointestinal tract
* Treatments can cause secondary health problems, such as infections, secondary forms of cancer, and heart disease
* There is a high risk of relapse and a low percent of long-term survival

## Extranodal NK/T-Cell Lymphoma, Nasal type Treatment

Once a definitive diagnosis of NK/T Cell Lymphoma, Nasal type has been made, staging is performed to determine how far the cancer has spread. The stage can describe:

* How many lymph nodes are affected (if any)
* Their locations in the body
* And, if other organs are being affected

Staging is important because different treatment regimens are necessary, depending on the progression of the lymphoma.

* Stage 1E: Single extranodal site involvement (generally the nose or nasal passage), and there may or may not be extension into nearby structures
* Stage 2E: In addition to stage 1 symptoms, there can be involvement of the lymph nodes and additional sites, including the head and neck
* Stage 3E: This rare stage includes stage 1 symptoms, involvement of lymph nodes above and below the diaphragm, and spleen involvement may be observed
* Stage 4: Stage 1 disease symptoms, involvement of other organs, including the liver; and involvement of the bone marrow

A combination of treatments is used to most effectively treat this cancer. The aggressiveness of the treatment is determined by the disease progression.

Chemotherapy: This approach uses a combination of drugs to kill the cancerous cells and is most commonly used for NK/T Cell Lymphoma, Nasal type that has spread beyond the nasal passages.

* Commonly, the drug combination CHOP is used first, which includes doxorubicin, vincristine, cyclophosphamide, and prednisolone
* There can be severe side effects including fatigue, nausea, hair loss, anemia, high risk of infection, and drug-specific reactions
* Many T-cell lymphomas can be resistant to chemotherapy. It can also damage healthy cells
* Chemotherapy can be administered as a pill, liquid, shot, or intravenously. Although, this may work initially, and then stop being effective
* Chemotherapy can be administered prophylactically into the cerebral spinal fluid in the spinal cord, to prevent the spread of cancer to the central nervous system

Radiation: Radiation therapy is the use of high-energy radiation waves, to kill cancer cells by destroying their DNA.

* This treatment is commonly used, when ENKL is confined to the nasal passages and can be used in combination with chemotherapy
* The radiation may be administered by a machine placed outside the body, or by putting a radioactive material inside the body. An external beam targeted at the nasal passages is most commonly used for NK/T Cell Lymphoma, Nasal type
* The side effects of radiation therapy include nausea, vomiting, fatigue, pain, risk of (a different type of) cancer later in life, and a risk of heart disease
* Radiation can damage healthy cells in addition to cancer cells, causing further complications

Stem cell transplant: Blood stem cell transplants from stem cells, harvested from a compatible donor, or from the patient before treatment, can be used to help treat ENKL. This is more frequently used, if the cancer has relapsed or does not respond to other treatment methods.

Supportive treatment: Steroids, blood transfusions, anti-nausea medications, and antibiotics, may also be used. In combination with other treatment measures, these can help combat the symptoms of immune deficiency.

Clinical trials: There are some new treatment options, currently on clinical trials that can be considered for some patients, depending on their risk factors.

## Extranodal NK/T-Cell Lymphoma, Nasal type Prevention

* Currently, there are no definitive ways to prevent Extranodal NK/T Cell Lymphoma, Nasal type
* However, healthy diet and exercise, as well as avoidance of unnecessary exposure to chemicals, may help decrease its risk
* Regular medical screening at periodic intervals with blood tests, scans, and physical examinations, are mandatory for those who have already endured the tumor, due to its metastasizing potential and possibility of recurrence. Often several years of active vigilance is necessary

## Prognosis of Extranodal NK/T-Cell Lymphoma, Nasal type

* The prognosis of Extranodal NK/T Cell Lymphoma, Nasal type is generally poor. This particular type of cancer is an aggressive form of NK/T-cell Lymphoma, with a high risk of relapse
* Without proper treatment of ENKL, the survival period is often no longer than a few months
* With treatment, the progression of the cancer affects the prognosis. Over 60% of those with stage I diseases have a long-term remission; but those with late stage disease, often have a survival rate of a few years at the most

Epidemiology of Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKTL-NT):

* Geographic and Ethnic Distribution:
  + ENKTL-NT is an aggressive extranodal non-Hodgkin lymphoma most commonly found in East Asia (e.g., China, Japan, Korea) and Latin America (e.g., Mexico, Brazil, Guatemala), where it can represent up to 10–15% of all non-Hodgkin lymphomas (NHL).
  + In contrast, it is rare in the United States, Canada, and Europe, accounting for less than 1% of NHL cases in these regions.
  + In the U.S., it represents about 0.2% of all NHL and approximately 1–2% of all T/NK-cell lymphomas.
  + Incidence is significantly higher among Asian Pacific Islanders (API) and Hispanics compared to non-Hispanic Whites.
* Incidence Rates:
  + Age-adjusted incidence rates reported are approximately 0.04 per 100,000 persons in the U.S. and about 0.1 per 100,000 in Japan.
  + Registry data show an increasing incidence trend in the U.S., with an estimated relative increase of up to 10% per year in recent years.
* Demographics:
  + ENKTL-NT shows a male predominance.
  + Median age at diagnosis is around 53 years, though this can vary by population.
  + Familial cases are rare but have been reported, with some environmental risk factors such as pesticide exposure suggested.
* Clinical Presentation:
  + Most patients present with localized disease (stage I/II) involving the nasal cavity and upper aerodigestive tract.
  + Extranasal and disseminated forms have poorer prognosis and are less common.
* Survival:
  + The estimated 5-year overall survival ranges between 40% and 50%, heavily dependent on stage at diagnosis and disease dissemination.

REFERENCES

<https://pmc.ncbi.nlm.nih.gov/articles/PMC5199232/>

<https://seer.cancer.gov/seertools/hemelymph/51f6cf56e3e27c3994bd530f/>

### Hemophilia A

Hemophilia A (classic hemophilia) is one of three types of hemophilia. Hemophilia is a rare blood disorder that happens when your blood doesn’t clot as well as it should. People who have this condition don’t have enough of a certain blood protein (clotting factor) that helps make blood clot. Hemophilia A usually affects men, but can also affect women.

Healthcare providers currently treat this condition by replacing the missing clotting factor. Providers are also researching gene therapy and gene replacement therapy as new ways of treating hemophilia A and other forms of hemophilia.

### How does hemophilia A affect my body?

People can be born with mild, moderate or severe forms of hemophilia A. People who have mild or moderate hemophilia A may have trouble controlling bleeding after being injured or having surgery. People who have severe hemophilia A may develop spontaneous bleeding into their joints that’s very painful and affects their ability to get around. Bleeding in other sites of your body is also possible.

### Is hemophilia A common?

No, hemophilia A and all other types of hemophilia are rare disorders. Healthcare providers estimate about 12 in 100,000 males in the United States have hemophilia A.

#### What are other hemophilia types?

Hemophilia type B and type C are other hemophilia types. Like hemophilia A, types B and C happen when genetic mutations affect blood-clotting proteins that help slow or stop bleeding.

#### Is hemophilia A worse than hemophilia B?

Studies show hemophilia B may be less serious than hemophilia A. Hemophilia B is still a serious medical condition, but people who have this form of hemophilia may have fewer problems with excessive bleeding. Here are some other differences between hemophilia A and B:

* Studies show people who have hemophilia B have fewer hemarthrosis, or bleeding into their joints, and less joint damage from that bleeding into their joints.
* People with hemophilia B have fewer episodes of spontaneous bleeding, meaning bleeding that happens without apparent cause.
* Sometimes, people treated for hemophilia develop problems with antibodies that interfere with treatment. Studies show people who have hemophilia B are less likely to develop these issues.

## Symptoms and Causes

Our bodies have 13 clotting factors, or proteins, that work together to form a blood clot. If you have hemophilia A, you’re missing factor VIII, a blood protein that helps your blood to form clots.

Normally, a gene called *F8* carries instructions on how to create factor VIII. Hemophilia A happens when that gene mutates and becomes an abnormal gene that makes a faulty version of factor VIII or doesn’t make factor VIII at all. About 70% of people who have hemophilia A inherited the disorder. But 30% of people with hemophilia A develop the disorder spontaneously, meaning they don’t have a family history of hemophilia.

Men inherit hemophilia if their biological mothers carry the condition. Here’s how that happens:

* The *F8* gene sits on the X chromosome.
* Women inherit two X chromosomes, one each from their mother and father.
* Men inherit an X chromosome from their mother and a Y chromosome from their father.
* If a woman has an abnormal *F8* gene on one of their X chromosomes, they carry hemophilia, but they won’t have symptoms. That’s because there’s a normal *F8* gene on their second X chromosome.
* They can pass the chromosome carrying the abnormal *F8* gene on to their sons. Because men have just one X chromosome, their sons will develop hemophilia. Men can’t pass hemophilia on to their sons, though.
* If a woman has a daughter, they may also pass this chromosome on to that child. Because women have two X chromosomes, their baby is likely to inherit a healthy X chromosome from their father.
* Women who inherit a healthy chromosome and a chromosome carrying the mutated *F8* gene can pass the gene on to their children. These people are sometimes referred to as carriers.

### Can women develop hemophilia, including hemophilia A?

They can, but symptomatic hemophilia in women is much less common than symptomatic hemophilia in men. Some women have hemophilia because both X chromosomes are affected, or one chromosome is affected and the other isn’t functioning enough. They may have the same hemophilia symptoms as men, but they’re more likely to have a mild form of hemophilia and less serious symptoms. That said, women who have hemophilia may have unusually heavy or prolonged periods (menstrual cycles), heavy bleeding after giving birth and other medical issues.

### What are hemophilia A symptoms?

Hemophilia A symptoms vary depending on whether the condition is mild, moderate or severe. About half of all people with hemophilia A have a severe form of the condition.

#### Mild symptoms

People who have factor VIII levels of more than 5% up to 40% have mild hemophilia A and mild symptoms. In this case, people may not have any symptoms until they’re adults. Some people don’t notice symptoms unless they need surgery, are injured or have dental procedures. In those circumstances, the most common symptoms are bleeding more than expected after surgery, being injured or having dental treatment. People may also have bleeding that lasts longer than expected.

#### Moderate symptoms

People who have factor VIII levels between 1% and 5% have moderate hemophilia A and moderate symptoms. Moderate hemophilia A symptoms typically surface when children are toddlers. They may have the following symptoms:

* Bruising: They bruise very easily.
* Unusual bleeding: If they have surgery, have an injury that causes bleeding or have a tooth pulled, they’ll bleed more than normal and for a longer time than expected.
* Spontaneous bleeding: Rarely, they’ll begin to bleed for no apparent reason.

#### Severe symptoms

People who have less than 1% of factor VIII in their blood have severe hemophilia A and severe symptoms. Many times, hemophilia A symptoms appear as children are being born or, in the case of male babies, when they’re being circumcised. Other times, children develop symptoms a few months after they’re born. Common symptoms include:

* Bleeding: Babies and toddlers may bleed from their mouths after minor injuries, like bumping their mouths on a toy.
* Swollen lumps on their heads: Babies and toddlers who bump their heads often develop goose eggs — large round lumps on their heads.
* Fussiness, irritability or refusing to crawl or walk: These symptoms may happen if babies and toddlers have internal bleeding into a muscle or joint. They may have areas on their bodies that look bruised and swollen, feel warm to your touch or cause pain when you gently touch the area.
* Hematomas: A hematoma is a mass of congealed blood that gathers under babies’ or toddlers’ skin. Babies and toddlers may develop hematomas after receiving an injection.
* Breathing difficulties: Sometimes, bleeding may cause your child’s tongue to swell so much that it blocks their airway.

## Diagnosis and Tests

Healthcare providers use blood tests to diagnose this condition. Those tests include:

* Complete blood count: Healthcare providers use this test to measure and study blood cells.
* Prothrombin time (PT) test: Healthcare providers use this test to see how quickly your blood clots.
* Activated partial thromboplastin time test: This is another blood test to time blood clot formation.
* Fibrinogen test: This is a blood test to measure the amount of blood protein fibrinogen, which helps with clotting.
* Clotting factor test: This blood test shows the hemophilia type and severity.

## Management and Treatment

Healthcare providers typically treat hemophilia A with factor replacement therapy. If you’re receiving this treatment, your healthcare providers will inject concentrated factor VIII into your bloodstream. Factor VIII replaces the missing blood protein, or factor, that helps blood to clot, so you’re less likely to have excessive bleeding and/or be able to control bleeding when it happens.

Usually, people with mild or moderate hemophilia A don’t need replacement therapy unless they’re going to have surgery or if they’re dealing with a bleeding episode. Healthcare providers often treat people who have severe hemophilia A with regular factor replacement therapy.

Another treatment option is a drug called emicizumab, which is a monoclonal antibody that substitutes the normal function of factor VIII.

#### What are replacement therapy complications?

People receiving replacement therapy may develop complications, including inhibitors and viral infections.

#### Inhibitors

People develop inhibitors when their bodies stop accepting the factor treatment as part of their normal blood. Inhibitors prevent factor treatment from working, which may make it difficult to slow or stop bleeding episodes. About one-third to one-fifth of people who have severe hemophilia A may develop inhibitors. People are more likely to develop this complication if they have severe bleeding disorders and are receiving high doses of factor replacement therapy. Healthcare providers may treat this complication by using a higher dose of replacement therapy or a different replacement therapy.

#### Viral infections

Rarely, people may develop viral infections, particularly hepatitis C, if they receive clotting factors from human blood. This is much less common with current Red Cross screening procedures.

## Outlook / Prognosis

Most people receiving treatment have a good prognosis, or expected outcome. Studies show children who are treated for their hemophilia typically have a normal lifespan. People who have severe hemophilia A may develop other medical conditions that affect their overall health and lifespan. For example, bleeding into joints may lead to joint disease.

If you have hemophilia A, ask your healthcare provider what you might expect. They know your situation, including your overall health, and are the best resource for information.

#### What can I expect if my child has this condition?

If your child has mild or moderate hemophilia A, make sure healthcare providers know about the condition. That way, they can take steps to prevent excessive bleeding if your child needs surgery or dental treatment like having a tooth pulled. Here are some other suggestions. Your healthcare provider may have more:

* When your child is very little, you should make sure their high chairs and car seats have adequate safety straps.
* As they grow up and play with other children, their caregivers and teachers should know what to do if your child is accidentally hurt and starts bleeding.
* Your child may need to avoid certain activities, like sports where they’re likely to bump hard into other people or take hard falls.

#### My child has severe hemophilia A. What should I expect?

Children who have severe hemophilia A will need medical treatment for the rest of their lives, whether it’s treatment to prevent or slow bleeding or treatment to ease symptoms. Some potential challenges you may encounter, and some suggestions that may help, include:

* Babies and toddlers with hemophilia A may start bleeding simply by bumping into things or falling as they learn to walk. You can’t always prevent those tumbles but it may make sense to put protective covering on any sharp edges on furniture.
* As your child grows up and starts playing or running about, talk to your healthcare provider about protective gear like helmets and kneepads. Of course, all children should wear helmets when riding bikes. Your child may need extra protection to avoid bumps that could cause bleeding.
* Your child will probably need regular medical treatment to prevent bleeding. They may get frustrated and angry if their appointments for treatment mean they can’t be with their friends or miss school or social activities.
* A child who has hemophilia knows their teachers and other people are aware of their situation. They may feel awkward if teachers and other school staff try to be helpful by treating them differently.
* All children want to fit it in. Having a rare disease like hemophilia A may make children feel self-conscious about their illness. Older children and teenagers may need help coping with their feelings and managing their reactions to other people. If that’s your child’s situation, talk to your healthcare provider about programs or support groups for young people.

## Prevention

You can’t prevent hemophilia A because it’s an inherited condition.

#### I’m pregnant and carry hemophilia A. Can I find out if my baby has this condition before they’re born?

Yes, healthcare providers can take a sample of blood from your umbilical cord to test clotting factors. That way, you and they will know what to expect during delivery and take steps to prevent any complications bleeding may cause.

## Living With

Living with hemophilia A means being vigilant about treatment and taking extra steps to protect your overall health. Here are some suggestions:

* Protect yourself from infection: Ask your healthcare provider what vaccinations make sense.
* Aim for a healthy weight: Managing your weight may help if you’re having trouble getting around because internal bleeding damaged your joints.
* Develop an exercise routine: You may worry about hurting yourself during exercise. Talk to your healthcare provider about ways to reduce the risk of bleeding while staying active.
* Manage your stress: Hemophilia A is a lifelong illness. It may take extra effort to balance your obligations to your family and your work.
* Avoid certain pain medications: If you have hemophilia A, you shouldn’t take aspirin or ibuprofen. These pain medications interfere with blood clotting.

### When should I see my healthcare provider?

You should see your healthcare provider for your regular treatment and any time you have unusual bleeding or other symptoms like severe joint pain.

#### When should I go to the emergency room?

You should seek immediate medical help if you have a head injury. The following symptoms could mean you have brain bleed or hemorrhage (intracranial hemorrhage):

* Headaches.
* Weakness.
* Nausea and vomiting.
* Numbness or paralysis.

Contact your healthcare provider or go to the emergency room any time you can’t stop bleeding from any kind of injury or if you start to bleed for no apparent reason.

**DIFFERENTIAL DIAGNOSIS**

* Acquired hemophilia
* Ehlers-Danlos syndrome
* Factor XI deficiency
* Glanzmann thrombasthenia
* Haemophilia C
* Haemophilia type B
* Physical child abuse
* Platelet disorders
* Von Willebrand disease

**Epidemiology of Hemophilia A**

Global Prevalence:

Recent meta-analyses estimate that over 1,125,000 males worldwide have hemophilia (both A and B), with about 418,000 having severe hemophilia; this is approximately three times higher than previous estimates of around 400,000 total cases.

Hemophilia A, caused by factor VIII deficiency, is the most common form, accounting for about 80–85% of all hemophilia cases.

Incidence:

Hemophilia A occurs in approximately 1 in 5,000 male births globally.

Other sources estimate hemophilia overall occurs in about 1 in 6,000 to 10,000 males internationally.

The incidence at birth is consistent worldwide due to its genetic inheritance pattern.

Demographics:

Hemophilia A primarily affects males due to its X-linked recessive inheritance; however, female carriers may have mild symptoms or low factor VIII levels in 20–30% of cases.

All races and ethnic groups are affected equally.

Many patients remain undiagnosed, especially in developing countries where access to diagnosis and treatment is limited.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK470265/#article-22743.s9>

https://www.hemophiliafed.org/disease\_type/hemophilia-a/

[Hemophilia A: Definition, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/23197-hemophilia-a)

**HEREDITARY HEMORRHAGIC TELANGIECTASIA**

**DEFINITION AND DESCRIPTION**

Hereditary hemorrhagic telangiectasia (tuh-lan-jee-uk-TAY-zhuh) is a condition that's passed through families, called inherited. It causes atypical links between arteries and veins called arteriovenous malformations (AVMs). The most common sites AVMs affect are the skin, nose, digestive system, lungs, brain and liver.

AVMs may get larger over time. They can bleed or burst. This can result in serious complications, including death.

Nosebleeds that happen for no known reason are the most common symptom. Nosebleeds can happen every day. Ongoing bleeding from the nose and the intestinal tract can result in serious iron deficiency anemia and poor quality of life.

Also called Osler-Weber-Rendu disease and HHT, hereditary hemorrhagic telangiectasia passes from parents to children. How bad it is can vary greatly from person to person, even within the same family.

If you have HHT and have children, you may want to have them checked for the condition. HHT can affect them even if they don't have symptoms.

**Causes**

HHT is a condition of gene changes, called genetic, that you get from your parents. It is an autosomal dominant disorder. That means if one of your parents has HHT, you have a 50% chance of getting it. If you have HHT, each of your children has a 50% chance of getting it from you.

**Risk factors**

The major risk factor for hereditary hemorrhagic telangiectasia is having a parent with the condition.

**SYMPTOMS**

Symptoms of HHT include:

* Nosebleeds. These can happen every day. They often start in childhood.
* Lacy red vessels or tiny red spots, mostly on the lips, face, fingertips, tongue and inside the mouth. These are called telangiectasias.
* Iron deficiency anemia due to bleeding from the nose or intestinal tract.
* Shortness of breath.
* Headaches.
* Seizures.
* Pus-filled swelling in the brain, called a brain abscess, and strokes.
* Infection in a bone, called osteomyelitis.

**Diagnosis and test**

Your healthcare professional may diagnose HHT based on a physical exam, results of imaging tests and a family history. But some symptoms may not show up in children or young adults. Having genetic testing for HHT may confirm the diagnosis.

### Imaging tests

In HHT, atypical links called arteriovenous malformations, also called AVMs, happen between arteries and veins. HHT AVMs can be present in internal organs such as the lungs, brain and liver. One or more of the following imaging tests can help find AVMs:

* **Ultrasound.** This test can show whether the AVMs affect the liver.
* **MRI.** This scan can check for AVMs in the brain as well as the liver and other organs in the belly.
* **Echocardiogram bubble study.** During this echocardiogram test, a healthcare professional puts a line in a vein, called an IV. A small amount of air bubbles put into the IV lets the healthcare professional find and assess any lung AVMs.
* **CT scan.** These can confirm AVMs in the lungs, the liver and other organs in the belly.

## Treatment

If you or your child has HHT, if you can, seek treatment at an HHT Center of Excellence. HHT is a rare condition that is best managed at centers that treat all aspects of this condition at every age. So it can be hard to find a specialist to treat it.

In the United States, Cure HHT names HHT Centers of Excellence for being able to diagnose and treat all aspects of the condition. Mayo Clinic is an HHT Center of Excellence and cares for many people and their family members diagnosed with HHT.

### Medications

Medicines that help stop the bleeding linked with HHT can be divided into three broad groups:

* **Hormone-related drugs.** Medicines that have estrogen can be helpful. But side effects are common with the high doses needed. Anti-estrogens such as tamoxifen (Soltamox) and raloxifene (Evista) also can control HHT.
* **Medicines that block blood vessel growth.** One treatment for HHT is bevacizumab (Avastin). Avastin goes through a tube in a vein, called intravenous. Other medicines healthcare professionals use to block blood vessel growth include pazopanib (Votrient), pomalidomide (Pomalyst) and tacrolimus (Prograf, Protopic, others).
* **Medicines that slow clot dissolving.** Tranexamic acid (Cyklokapron, Lysteda) can help stop serious bleeding in emergencies. If taken regularly, it may help prevent bleeding.

If you get iron deficiency anemia, you might get an iron replacement through a vein. This most often works better than taking iron pills.

### Surgical and other procedures for the nose

Serious nosebleeds are one of the most common signs of HHT. These sometimes happen daily. They can cause so much blood loss that you become anemic. You might need to receive blood, called a transfusion, and iron through an arm vein.

Procedures to lower the number of nosebleeds and lessen how bad they are may include:

* **Ablation.** This procedure uses energy from lasers or other devices to seal the vessels that cause the nosebleeds. But this most often is short-lived. The nosebleeds come back over time.
* **Skin graft.** Skin from another part of the body can be put inside the nose. The skin most often comes from the thigh. Healthcare professionals rarely do this procedure anymore because of how well newer medicines work.
* **Surgically closing the nostrils.** If nothing else works, joining flaps of skin within the nose to close the nostrils often is a success. This is done only when other treatments have failed. Healthcare professionals rarely do this procedure anymore because of how well newer medicines work.

### Surgical and other procedures for the lungs, brain and liver

HHT most often affects the lungs, brain and liver. Procedures to treat AVMs in these organs may include:

* **Embolization.** In this procedure, a healthcare professional threads a long, slender tube through the blood vessels to the AVM. Then the health professional puts in a plug or a metal coil to block blood from entering the AVM. This shrinks and heals the AVM over time. Embolization treats lung and brain AVMs, but not liver AVMs.
* **Surgical removal.** Rarely, the best way to treat certain AVMs in the brain or the lungs is to remove them with surgery.
* **Stereotactic radiotherapy.** This procedure treats AVMs in the brain. It uses beams of radiation that come from different directions. They meet at the AVM to treat it.
* **Liver transplant.** Rarely, treatment for AVMs in the liver is a liver transplant.

**Lifestyle and home remedies**

To help prevent HHT nosebleeds, you may want to:

* **Not use certain medicines.** Your risk of bleeding can be higher from using certain medicines and drugs you get without a prescription. These include aspirin, ibuprofen (Advil, Motrin IB, others), fish oil supplements, ginkgo and St. John's wort.
* **Not eat certain foods.** In some people, having blueberries, red wine, dark chocolate or spicy foods can cause HHT nosebleeds. Try keeping a food diary to see if there's any link between what you eat and how bad your nosebleeds are.
* **Keep your nose moist.** Use saline sprays, lotions or gels that add moisture to help lower the risk of bleeding. Using a bedside humidifier overnight also is helpful.
* **Not do heavy lifting.** Bending over and lifting heavy objects can cause nosebleeds.

### Complications

The complications of HHT can vary widely, even among people affected by HHT in the same family. Complications and treatment of HHT depend on the parts of the body that are affected by this disorder. Treatment may include controlling bleeding and anemia and preventing complications from abnormal artery-vein connections in the lungs and brain.

**DIFFERENTIAL DIAGNOSIS**

Bleeding from diseases like von Willebrand disease or hemophilia is more generalized and occurs in an injury setting. In contrast, bleeding from HHT is more localized to the malformed blood vessels. Several diseases share similar clinical manifestations to HHT and must be ruled out during the workup. Referral to a hematologist can prove very helpful.

**Limited Systemic Sclerosis**

Patients with limited systemic sclerosis, called CREST syndrome, develop calcinosis, Raynaud disease, esophageal dysmotility, sclerodactyly, and telangiectasias. However, recurrent epistaxis is not a common feature of the syndrome. Specific autoantibodies may be positive in scleroderma, including anti-centromere antibodies, anti-topoisomerase I (Scl-70), and anti-RNA polymerase III.

**Ataxia-Telangiectasia**

Ataxia-telangiectasia is an autosomal recessive condition that presents with cerebellar atrophy with progressive ataxia, cutaneous telangiectasias, immune defects, and increased risk for malignancies. Symptoms typically occur in the first or second decade of life. Key features of this condition include elevated serum alpha-fetoprotein (AFP) and decreased total IgG and IgA.

**Generalized Essential Telangiectasia**

Generalized essential telangiectasia is rare; inherited and sporadic cases have been reported. The telangiectasias first appear on the lower extremities and slowly spread to involve the entire body.

**Hereditary Benign Telangiectasia**

Hereditary benign telangiectasia is an autosomal dominant primary telangiectasia disorder with the development of telangiectasias on the skin and lips during birth or childhood. Lesions are usually asymptomatic and do not have systemic involvement. Unlike in HHT, histology of hereditary benign telangiectasia demonstrates preserved skin and dilated vessels with thicker capillary walls, explaining the lack of hemorrhage.

**Rosacea**

Rosacea is a common skin disorder with recurrent facial flushing, erythema, telangiectasias, and inflammatory pustules on the face. Etiological factors for the development of the condition include genetics, environmental factors, neurovascular deregulation, and microorganisms.

**Telangiectasia Macularis Eruptiva Perstans**

Telangiectasia macularis eruptiva perstans is a rare form of mastocytosis. The condition is seen more frequently in adults. Telangiectatic macules manifest as flat, reddish-brown lesions on the skin due to infiltration of mast cells into the upper dermis. Systemic involvement may involve the bone marrow, GI tract, liver, and lymph.

**Dermatomyositis**

Dermatomyositis is an idiopathic chronic inflammatory autoimmune disorder of the skin and muscles. Skin manifestations include heliotrope rash around the eyes, papules over digits, and periungual telangiectasias.

**Systemic Lupus Erythematosus (SLE)**

Lupus erythematosus is a multi-organ autoimmune disease with varying clinical presentations. Cutaneous manifestations include a malar rash, oral and nasal ulcers, and periungual telangiectasias

**Epidemiology**

HHT affects 1 in 5,000-8,000 individuals and can affect both genders and people of all races. Some studies have noted a higher incidence in women, although this gender difference may be attributed to access to healthcare resources

REFERENCES

[Hereditary Hemorrhagic Telangiectasia (HHT) - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK578186/#article-141559.s10)

[About Hereditary Hemorrhagic Telangiectasia (HHT) | Hereditary Hemorrhagic Telangiectasia (HHT) | CDC](https://www.cdc.gov/hht/about/index.html)

[Hereditary hemorrhagic telangiectasia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hht/symptoms-causes/syc-20351135)

## Histiocytic Sarcoma

### Pathology and Definition

## Histiocytic sarcoma is a malignant proliferation of histiocytes, which are part of the mononuclear phagocyte system. These cells are responsible for phagocytosis, or the process of engulfing and digesting cellular debris and pathogens. The disease can affect various organs and tissues, including lymph nodes, skin, and the gastrointestinal tract.

### Causes and Risk Factors

## The exact causes of histiocytic sarcoma remain largely unknown. However, certain genetic mutations and previous exposures to radiation or chemotherapy may increase the risk. Additionally, there is a documented association with other hematologic malignancies, such as leukemia and lymphoma.

## Symptoms of Histiocytic Sarcoma

### General Symptoms

## The symptoms of histiocytic sarcoma can vary widely depending on the affected organs. Common symptoms may include:

## Fever

## Fatigue

## Weight loss

## Night sweats

### Localized Symptoms

## Symptoms can also be localized depending on the specific organ involved:

## Lymph Nodes: Swelling and tenderness

## Skin: Nodules or ulcers

## Gastrointestinal Tract: Abdominal pain, nausea, vomiting and gastrointestinal bleeding

### Advanced Symptoms

## In more advanced stages, histiocytic sarcoma can lead to significant organ dysfunction, necessitating urgent medical intervention.

## Diagnostic Methods

### Radiology and Imaging

## Radiologic imaging plays a crucial role in diagnosing histiocytic sarcoma. Techniques such as CT scans, MRI, and PET scans are commonly used to identify the extent of the disease and guide biopsy procedures.

### Pathology and Biopsy

## A definitive diagnosis is often made through a biopsy, where tissue samples are examined under a microscope. Pathology outlines reveal specific features such as the presence of large, atypical histiocytes and the expression of certain markers like CD163 and CD68.

### Immunohistochemistry

## Immunohistochemical staining is essential for confirming the diagnosis. Markers such as CD163, CD68, and lysozyme are usually positive in histiocytic sarcoma, helping to distinguish it from other malignancies.

## Treatment Options

### Surgery

## Surgical resection is often the first line of treatment, especially for localized histiocytic sarcoma. Complete removal of the tumor can significantly improve prognosis.

### Chemotherapy

## Chemotherapy is commonly used, particularly in cases where the disease has metastasized. Regimens often include agents such as doxorubicin, cyclophosphamide, and vincristine.

### Radiation Therapy

## Radiation therapy can be effective in controlling local symptoms and reducing tumor size. It is often used in combination with surgery and chemotherapy for a more comprehensive treatment approach.

### Targeted Therapy

## Emerging treatments such as targeted therapy and immunotherapy are being explored. These treatments aim to specifically target cancer cells while minimizing damage to normal cells, offering a promising avenue for future treatment.

## Prognosis and Follow-Up

### Prognostic Factors

## The prognosis for histiocytic sarcoma varies depending on several factors, including the stage at diagnosis, the affected organs, and the patient's overall health. Early detection and comprehensive treatment can significantly improve outcomes.

**EPIDEMIOLOGY**

Epidemiology of Histiocytic Sarcoma (HS):

Rarity: Histiocytic sarcoma is an exceedingly rare hematologic malignancy[3](https://www.webpathology.com/images/hematopathology/myeloid-histiocytic-and-dendritic-cell-neoplasms/histiocytic-sarcoma/38357)[5](https://atlasgeneticsoncology.org/haematological/1724/histiocytic-sarcoma)[6](https://journals.sagepub.com/doi/10.1177/03009858231166658?icid=int.sj-abstract.similar-articles.3). It constitutes less than 1% of all hematolymphoid neoplasms[2](https://www.pathologyoutlines.com/topic/lymphnodeshistiocyticsarcoma.html)[6](https://journals.sagepub.com/doi/10.1177/03009858231166658?icid=int.sj-abstract.similar-articles.3).

Incidence: The overall incidence of histiocytic sarcoma is approximately 0.17 cases per 1,000,000 individuals.

Age Distribution:

HS usually occurs in adults.

The median age at diagnosis is generally in the sixth decade of life. Some data indicates this is approximately 51 years.

HS may exhibit a bimodal distribution, with increased frequency in individuals younger than 30 years and older than 50 years.

Race:

Incidence varies among racial groups.

Whites have a higher incidence compared to African Americans. One study reported the incidence among whites as 0.18 per 1,000,000, while for African Americans, it was 0.04 per 1,000,000.

Associations: Histiocytic sarcoma is associated with:

Non-Hodgkin's lymphomas, including lymphoblastic lymphoma, follicular lymphoma, and low-grade B-cell lymphoma

Germ cell tumors, such as mediastinal non-seminomatous germ cell tumors and primary gonadal germ cell tumors

**Differential Diagnosis of Histiocytic Sarcoma:**

Malignant entities: Anaplastic large cell lymphoma, B- or T-lineage large cell lymphomas, hepatosplenic T-cell lymphoma, follicular dendritic neoplasms, myeloid sarcoma (especially those with monoblastic differentiation), anaplastic carcinomas, and malignant melanoma.

Benign histiocytic entities: Infection associated hemophagocytic syndrome, familial hemophagocytic lymphohistiocytosis, storage diseases (Gaucher's and Niemann-Pick).

Both reactive histiocytic proliferations and histiocytic sarcoma can have hemophagocytosis, multinucleated cells, and foamy cytoplasm. Histiocytic sarcoma shows cytologically malignant nuclei in contrast to bland nuclear features of reactive histiocytic proliferations.

Interdigitating dendritic cell sarcoma shows histologic overlap with histiocytic sarcoma. Features favoring interdigitating dendritic cell sarcoma include relatively lower degree of nuclear pleomorphism, greater degree of cell spindling and stronger, diffuse positivity for S-100.

Anaplastic large cell lymphoma is the non-Hodgkin lymphoma most frequently confused with histiocytic sarcoma. The distinction of non-Hodgkin lymphomas from histiocytic sarcoma requires immunophenotypic analysis (by flow cytometry) and gene rearrangement studies. The presence of CD30 expression or expression of lineage specific T- or B-cell markers rules out histiocytic sarcoma.

The image shows histiocytic sarcoma of small bowel that caused intestinal obstruction. The patient presented to the emergency room with severe abdominal pain, nausea and vomiting. There was history of fever and progressive weight loss. The intestinal architecture is distorted by sheets of pleomorphic tumor cells with abundant eosinophilic cytoplasm. There is an infiltrate of eosinophils, lymphocytes, and plasma cells in the background

REFERENCES

<https://pmc.ncbi.nlm.nih.gov/articles/PMC5757688/>

<https://www.pathologyoutlines.com/topic/lymphnodeshistiocyticsarcoma.html>

### 

### Paroxysmal nocturnal hemoglobinuria (PNH)

**DEFINITION AND DESCRIPTION**

## Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder named for a single symptom: Red/brown/dark urine noticed during late night or early morning trips to the bathroom. “Paroxysmal” means sudden; “nocturnal” means night; and “hemoglobinuria” refers to pee stained with blood. Your pee is dark because your immune system is breaking down your red blood cells. Healthcare providers call this hemolysis.

## Dark-colored pee is only one of many PHN symptoms that may signal potentially serious illnesses. Left untreated, PNH may cause hemolytic anemia, chronic kidney disease or thrombosis (blood clots in your blood vessels). Healthcare providers treat PNH with medication that prevents blood cell damage.

### Who does it affect?

## About 6 per 1 million people are diagnosed with PNH each year. This condition affects men and women between the ages of 30 and 40. Women are slightly more likely than men to develop PNH. Often, people who have bone marrow disorders like aplastic anemia or myelodysplastic syndrome develop paroxysmal nocturnal hemoglobinuria.

### What is the difference between hemoglobinuria and hematuria?

## Both conditions cause blood in your urine. The difference is hematuria is red blood cells in your urine, while hemoglobinuria is hemoglobin in your urine. Hemoglobin is a protein in your red blood cells that makes blood look red.

## Causes

## PNH happens when a genetic flaw affects how your red blood cells and platelets work. The flaw launches a cascade of events that create serious and potentially life-threatening medical issues.

## The cascade starts in your bone marrow, where your body makes stem cells that eventually become mature red blood cells, white blood cells and platelets. In PNH, a gene called *PIGA* in one stem cell mutates or changes into an abnormal stem cell. This cell divides and makes additional abnormal stem cells that become abnormal red blood cells and platelets.

#### How does genetic change affect red blood cells?

## Occasionally, proteins that help your white blood cells fight infection turn on your red blood cells. Healthcare providers refer to these proteins as the complement system.

## Normal red blood cells have a protective shield of proteins that fends off complement system assaults. The *PIGA* gene is responsible for the red blood cells’ protective shield. When the *PIGA* gene mutates, it stops making the protective shields. Here’s what happens next:

## When your complement system attacks your red blood cells, your red blood cells fall apart and release hemoglobin. Hemoglobin helps your red blood cells carry oxygen throughout your body. When red blood cells fall apart, they dump their hemoglobin into your bloodstream. Healthcare providers call this free hemoglobin.

## Normally, a substance called haptoglobin sweeps in and clears out free hemoglobin. But with PNH, your bloodstream cleaning crew can’t keep up.

## Your body also tries to manage the overflow with nitric oxide, but ends up depleting your body’s supply of it. Without enough nitric oxide, you may have sudden painful spasms in your stomach muscles, esophagus and muscles in your back.

## At the same time, your bone marrow is under pressure to make more red blood cells to replace those destroyed by your complement system. Anemia happens when your bone marrow can’t make enough red blood cells to compensate for the blood cells destroyed by your complement system.

## The overflow of hemoglobin also damages your kidneys. People who have PNH are six times more likely to develop chronic kidney disease.

## Free hemoglobin also affects your pee (urine). Many people who have PNH notice dark-colored pee during the night or first thing in the morning. That’s because excess hemoglobin becomes concentrated in pee, turning it dark.

#### How does genetic change affect platelets?

## Platelets are blood cells that help your body make blood clots. The mutated *PIGA* gene also affects stem cells that become abnormal platelets. The abnormal platelets make your blood clot more than it should. As a result, people who have PNA have an increased risk of life-threatening thrombosis or blood clots.

### Symptoms

## While paroxysmal nocturnal hemoglobinuria is named for one symptom, people who have PNH typically seek medical help because they have severe and persistent fatigue or tiredness that affects their daily lives. Other symptoms include:

## Shortness of breath (dyspnea).

## Kidney problems.

## Difficulty swallowing (dysphagia).

## Esophageal spasms.

## Stomach pain.

## Back pain.

## Erectile dysfunction.

## Diagnosis and Tests

### How do healthcare providers diagnose paroxysmal nocturnal hemoglobinuria?

## Healthcare providers may use several tests to look for signs of PNH. Based on those test results, they may use a test called flow cytometry to examine your blood cells. Tests healthcare providers might use include:

## Complete blood count with differential (CBC w/diff): Healthcare providers look for signs of blood disorders like anemia and thrombocytopenia and anemia.

## Basic metabolic panel (BMP): Healthcare providers look for signs of chronic kidney disease and renal dysfunction.

## Urinalysis: This test may show signs of hemoglobinuria (blood in pee) and hemosiderosis (excess iron deposits).

## 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.

## Liver function: This test measures bilirubin levels that may increase when red blood cells break down.

## Management and Treatment

## Healthcare providers use targeted therapies called complement inhibitors that keep your complement system from destroying red blood cells.

## Before this therapy was available, people with paroxysmal nocturnal hemoglobinuria needed regular red blood cell transfusions to treat anemia caused by PNH. At that time, people with PNH usually lived 10 to 22 years after their diagnosis. The only cure for PNH was to have an allogeneic stem cell transplant. Now, studies show people who receive this treatment can expect to live as long as someone who doesn’t have PNH.

### What are the treatment side effects?

## Complement inhibitors have many side effects. Fortunately, these side effects wear off soon after people start treatment.

## Outlook / Prognosis

## There are treatments that stop PNH from damaging your red blood cells and platelets. Most people who have PNH develop anemia that requires additional treatment.

## Prevention

## A genetic mutation causes PNH, which means you can’t prevent it.

## Living With

## Even with treatment, people who have PNH need to take steps to prevent blood clots. For example, people who have PNH and need surgery are at risk for blood clots and serious bleeding during surgery. People who are pregnant and have PNH face health risks that affect them and the developing fetus.

## Epidemiology

Paroxysmal nocturnal hemoglobinuria (PNH) incidence is estimated at 1–1.5 cases per million individuals worldwide, but might be higher in certain regions. The disease occurs more frequently in countries in Asia (for example, Japan, Korea and China) than in western countries (the United States, Spain and the United Kingdom).

The rarity of PNH has prompted the establishment of registries for collecting information about the disease. The International PNH Registry was established in 2003 to collect comprehensive data on the natural history of PNH and can provide some epidemiology data. Patients of any age with a clinical diagnosis of PNH (by any applicable diagnostic method) or a detectable fraction of PNH-affected blood cells (that is, a PNH clone) of ≥0.01% of all blood cells are eligible for inclusion.

As of June 30, 2012, 1610 patients from 273 centers in 25 countries were enrolled; of these patients, 92.5% were from Europe and North America and 87.5% were of White ethnicity. No definitive biological data exist to fully explain this distribution; furthermore, there may be bias in the registry. The remaining patients were of Asian or Pacific Island descent (5%), African descent (3.5%), native/Aboriginal descent (0.2%), or of other or unknown ethnicity (3.9%).

## Differential Diagnosis

Other Hemolytic Anemias:

* + Autoimmune Hemolytic Anemia (AIHA): Usually Coombs-positive; extravascular hemolysis predominates; lacks PNH clone.
  + Paroxysmal Cold Hemoglobinuria (PCH): Cold antibody-mediated hemolysis; Donath-Landsteiner test positive; hemolysis triggered by cold exposure.
  + Hereditary Spherocytosis / Elliptocytosis: Congenital membrane defects; family history; negative for PNH clone.
  + G6PD Deficiency: Episodic hemolysis triggered by oxidative stress; enzyme assay diagnostic.
  + Sickle Cell Disease: Hemoglobin electrophoresis diagnostic; vaso-occlusive crises prominent.

Bone Marrow Failure Syndromes:

* + Aplastic Anemia: Pancytopenia with hypocellular marrow; may coexist or precede PNH clone emergence.
  + Myelodysplastic Syndromes (MDS): Dysplastic marrow with cytopenias; chromosomal abnormalities; no PNH clone.

Thrombotic Disorders:

* + Mesenteric Artery Ischemia/Thrombosis: Acute abdomen; no hemolysis or PNH clone.
  + Portal Vein Thrombosis: May occur in PNH but also in cirrhosis, malignancy, or hypercoagulable states.

Other Causes of Hemoglobinuria:

* + Hematuria: Urine microscopy differentiates from hemoglobinuria.
  + Rhabdomyolysis: Myoglobinuria rather than hemoglobinuria; elevated CK levels.

Iron Deficiency Anemia:

* + Chronic blood loss; microcytic anemia; no hemolysis or PNH clone.

Anemia of Chronic Disease:

* + Normocytic or microcytic anemia; associated with chronic inflammation; no hemolysis.

REFERENCE

## [Paroxysmal Nocturnal Hemoglobinuria (PNH): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/22871-paroxysmal-nocturnal-hemoglobinuria)

<https://emedicine.medscape.com/article/207468-overview#a7>

### 

### 

### 

### Plasmacytoma

**Definition and description**

Plasmacytoma is a very rare condition that is similar to multiple myeloma. Like multiple myeloma, plasmacytoma happens when plasma cells, sometimes called B cells, turn into abnormal cells that multiply and become single tumors that affect your bones, soft tissues in your head and neck, or any organ in your body like your bladder, lung or kidney. There are two types of plasmacytomas — solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EMP).

### How do plasmacytomas affect my body?

Like multiple myeloma, plasmacytomas develop when healthy plasma cells turn into abnormal cells. Plasma cells are white blood cells and are part of your immune system. Healthy plasma cells (sometimes called B cells) make antibodies. These antibodies, called immunoglobulins, help fight infection and protect against illness. When healthy plasma cells become abnormal, they multiply and produce abnormal antibodies called M proteins. When M proteins multiply, your body has fewer normal plasma cells helping to protect against infection.

There are plasmacytoma types that can affect different parts of your body:

* Solitary plasmacytoma of bone (SPB): This happens when abnormal plasma cells form a tumor on one spot or site on one of your bones. SPB causes bone damage and pain. Approximately 50% of people who have SPB develop multiple myeloma.
* Extramedullary plasmacytoma (EMP): In EMP, a single tumor made of abnormal plasma cells affects soft tissue. Soft tissue connects, supports and surrounds your organs and bones. Your muscles, tendons, skin, fat and layers of connective tissue called fascia are examples of soft tissue. EMP can affect soft tissue throughout your body but typically affects your upper respiratory tract, which includes your nasal cavity, sinuses, nasopharynx and larynx, but can affect any organ. Approximately 15% of people who have EMP develop multiple myeloma.

### Who is affected by plasmacytomas?

Plasmacytomas typically affect people ages 55 to 60. Males are more likely to develop plasmacytomas than females.

### How common are plasmacytomas?

Plasmacytoma is very rare. Each year, healthcare providers diagnose 450 cases of SPB and approximately 300 cases of EMP. However, people who've been battling multiple myeloma for some time may also develop plasmacytomas.

## Symptoms and Causes

Solitary plasmacytomas of bone cause bone pain or bone fracture. Other SPB symptoms include:

* Pain or bone fractures in your rib bones, thoracic vertebrae, femur and pelvis.
* Compression fractures in your spine, which may damage your spinal cord or nerve root. This can cause sharp, stabbing pains that may shoot down your legs and spine.
* Rarely, SPB can affect your skull, causing headaches, dizziness and vision problems.

### What are EMP symptoms?

Extramedullary plasmacytoma symptoms may happen when the tumor presses on soft tissue, causing pain or affecting how your body functions. For example, an EMP in your nose may feel like there’s something stuck there that makes it hard for you to breathe through your nose. EMP may appear anywhere in your body, but 80% to 90% of EMPs appear in your head and neck. EMP symptoms include:

* Headache.
* Nasal discharge.
* Dysphagia (difficulty swallowing).
* Pharyngitis (sore throat).
* Epistaxis (nosebleed).

Rarely, EMP may affect your larynx (voice box), causing the following symptoms:

* Hoarseness.
* Obstructed airway.
* Wheezing.

Many plasmacytoma symptoms resemble common problems that may not be signs of serious illness. That said, you should contact your healthcare provider anytime you have symptoms that last longer than two weeks or get worse.

### causes of plasmacytomas

Plasmacytomas develop when healthy plasma cells turn into abnormal cells. Researchers don’t know what triggers this change.

## Diagnosis and Test

Healthcare providers use several tests to diagnose the different plasmacytoma types. They use what they learn to establish EMP stages.

* Computed tomography (CT) scan: This test uses a series of X-rays and a computer to produce a 3D image of soft tissues and bones. Providers use CT scans to look for possible bone damage caused by plasmacytoma.
* Magnetic resonance imaging (MRI): This test produces detailed images of your body without using radiation. Providers use MRI to evaluate soft tissue damage caused by EMP.
* Blood tests and urine test: Providers measure M protein levels with these tests.
* Nasal endoscopy: Providers may use this test to examine your nasal passages and sinus for signs of EMP.
* Fine-needle biopsy: Providers may use this test to obtain tissue and fluid from soft tissues affected by EMP.
* Biopsy. Providers may obtain tissue or fluid to examine plasma cells.

#### EMP stages

Healthcare providers use the following factors to stage extramedullary plasmacytoma:

* Stage I: Tests show a single tumor in one spot in your body.
* Stage II: Tests show EMP cells in your lymph nodes.
* Stage III: Tests show more than one EMP tumor.

## Management and Treatment

Healthcare providers treat solitary bone plasmacytoma with radiation therapy. (Providers often use multiple myeloma treatment in cases where people have abnormal proteins in their blood or urine and a plasmacytoma. Providers may treat extramedullary plasmacytoma with surgery and/ or chemotherapy or immunotherapy.

## Outlook / Prognosis

Approximately 60% of people who have SBP are alive five years after diagnosis. Approximately 82% of people who have EMP are alive five years after diagnosis. Unfortunately, plasmacytomas can come back or develop in another part of your body.

Some people who have SBP or EMP develop multiple myeloma. This affects how long they may live.

## Prevention

Like multiple myeloma, there’s no known way to prevent plasmacytoma.

## Living With

Plasmacytoma can become multiple myeloma. If you have plasmacytoma, you'll need life-long follow-up care once you complete treatment. Follow-up care typically includes regular blood and imaging tests, so healthcare providers can watch for signs of multiple myeloma. If you have plasmacytoma, ask your healthcare provider what follow-up care you can expect.

**DIFFERENTIAL DIAGNOSIS**

Plasmacytoma shows a few similarities with other diseases and hence needs to be differentiated from them. Differential diagnosis of plasmacytoma includes:

**Multiple Myeloma (MM)**

Multiple myeloma is a tumor of plasma cells. Plasmacytoma may progress to multiple myeloma over 2-3 years. Plasmacytoma is a localized bone disease and is further differentiated from multiple myeloma by the presence of CRABS (hypercalcemia, renal failure, anemia, bone disease), multiple lytic bone lesions, end-organ damage, and serum or urinary monoclonal proteins.

**Non-Hodgkin Lymphoma (NHL)**

NHL, in some cases, shows plasmacytic differentiation, which makes it difficult to differentiate them from plasmacytoma. In these cases, immunophenotyping can be used to differentiate these entities—plasma cells in lymphoma express CD19 and CD45. The phenotype of SPB lesion is similar to that of myeloma, but that of EMP lesion is similar to lymphomas suggesting that they may represent NHL with plasmacytic differentiation.

**Reactive Plasmacytosis**

It consists of follicular hyperplasia. There is no light chain restriction in reactive plasmacytosis as compared to plasmacytoma.

**Plasmablastic Lymphoma**

The tumor has plasmablastic morphology, often occurs in HIV-positive or immunosuppressed individuals. It occurs in the oral cavity or the mucosal surfaces of the head. It is associated with the Epstein-Barr virus

EPIDEMIOLOGY

Plasmacytoma is a rare disease, with SPB being the most common type. Solitary plasmacytoma has an annual incidence of fewer than 450 cases. The incidence of SPB is 40% more than EMP, with SPB constituting 2% to 5% of all plasma cell malignancies and EMP constituting 4% of all plasma cell malignancies.Plasmacytoma is prevalent in older individuals, African Americans, and males. It presents in the middle to old aged people with the mean age of presentation of 55 to 60 years.Plasmacytoma is more prevalent in males than females, with a male to female ratio of 2 to 1 in SPB and 3:1 in EMP.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK573076/#article-135195.s10>

[Plasmacytoma: What it Is, Treatment, Symptoms & Types](https://my.clevelandclinic.org/health/diseases/22826-plasmacytoma)

**T-Cell Prolymphocytic Leukemia**

In individuals with T-PLL, mutations in T-cell genes disrupt typical cell maturation, leading to uncontrolled growth and division. This causes cancerous cells to multiply rapidly and spread throughout the body, crowding out healthy cells.

This rare form of leukemia accounts for approximately 2% of adult mature lymphocytic leukemias. It most often affects people older than 65 years, although it can affect individuals in their 30s to 90s.

T-PLL is a rare and aggressive type of blood cancer that affects T cells, a type of white blood cell. These cells are part of the immune system that helps fight infection.

In people with T-PLL, changes or mutations in T-cell genes disrupt typical cell maturation and cause the cells to grow uncontrollably and rapidly. The number of immature, nonfunctional T cells increase, making it difficult for the body to produce new, healthy blood cells.

## Signs and symptoms

As a result of these cellular changes, a person develops various signs and symptoms. Common signs of T-PLL include:

* swollen lymph nodes
* enlarged liver and spleen
* night sweats
* weight loss
* fatigue
* weakness
* skin lesions or rashes
* high white blood cell counts
* low red blood cell counts, or anemia
* low platelet counts

## Causes

Doctors do not know the exact cause of T-PLL. However, it appears to involve certain mutations in T-cell genes that trigger typical T-cells to become leukemia cells.

The most common DNA changes are in proto-oncogene TCL-1, a cell growth and division gene. The genetic mutations turn it into an oncogene, which can trigger the growth of cancer cells.

Certain people, such as males and those over 65 years, are more likely to develop T-PLL. However, unlike other cancers, no known environmental risk factors exist.

## Survival rate

T-PLL is aggressive, and the outlook is generally unfavorable.

The overall survival rate for T-PLL varies depending on several factors, including the individual’s age, general health status, and the extent of the genetic abnormalities.

The survival time for individuals with T-PLL is typically less than 2 years from diagnosis, although some individuals may survive longer with appropriate treatment.

## Diagnosis and test

Diagnosing T-PLL is complicated and typically involves several steps to confirm the presence of the disease and determine its extent. The initial evaluation often includes a physical examination and blood tests.

These tests assess the levels of blood cells, including T lymphocytes, and look for signs of anemia or other abnormalities.

Doctors may use the following tests to diagnose PLL:

* Bone marrow biopsy: This checks if the bone marrow is healthy or making atypical cells.
* Peripheral blood smears: These check for T-cell changes.
* Immunophenotyping: This looks for markers on the surface of leukemia cells.
* Chromosome analysis: This checks to see if there are genetic changes.
* Imaging studies: These assess the extent of the disease.

## Treatment

T-PLL treatment involves a combination of therapies to control and manage the disease’s symptoms. The specific treatment approach depends on several factors, including the individual’s age, overall health status, and the extent of the disease.

Current treatment approaches include:

* Watching and waiting: Around 10–15% of those with T-PLL do not have symptoms during diagnosis. Therefore, doctors may delay treatment and monitor the individual to check for disease progression.
* Medications: For people with symptomatic T-PLL, drugs, including intravenous alemtuzumab (Campath) and alemtuzumab plus pentostatin (Nipent), may help control the disease.
* Hematopoietic stem cell transplantation: Doctors may suggest a stem cell transplant in people who achieve disease remission following drug therapy. This is the only treatment that may offer a potential cure.

People with T-PLL should explore all available treatment options, including participating in clinical trials. These offer access to new and innovative therapies that can help improve outcomes for individuals with this disease.

Clinical trials may involve testing new drugs, drug combinations, or dosing schedules, allowing people to benefit from new therapies that may not yet be widely available.

## Contacting a doctor

T-PLL is an aggressive cancer that requires timely diagnosis and treatment.

If someone experiences symptoms relating to T-PLL, they should contact their doctor immediately for evaluation. Early diagnosis and treatment can help improve outcomes for those with the disease.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of T-PLL includes other lymphoid neoplasms with a leukemic presentation; some relevant entities include :

* B cell prolymphocytic leukemia (B-PLL); B-PLL, compared to T-PLL, has minimal lymphadenopathy and rarely involves skin involvement. It shows a strong B-cell marker study (CD19, CD20, CD22) with additional positive markers of CD79a and CD5. CD23 is negative. The cytogenetics shows no t(11;14), but there is positivity for 13q del, 11q del, 17p del, or 6q del. The median survival in B-PLL is 3 years, measured in months for T-PLL. Cytologically, they bear a single prominent nucleolus.
* Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL): The cells are variably positive for CD5 and CD23 and weakly positive for CD22 and CD79b. They are CD10 negative. The cytogenetic analysis shows 13q del, 11q del, 17p del, or trisomy 12.
* Mycosis fungoides (MF) / Sezary syndrome (SS): Cells in Sezary syndrome are positive for CD2 and CD3. They are predominantly positive for CD4. They are positive for CD25 and negative for TCL1. They are usually negative for CD7 and CD26. Skin lesions may be found in as many as 20% of patients. A skin biopsy may be needed to exclude Sezary syndrome. The rash in SS is felt to be the harbinger of its lymphocytosis.
* Adult T cell lymphoma/leukemia (ATLL): Chronic HTLV-1 infection is thought to be the etiology of this neoplasm. HTLV-1 PCR/serology is positive; T-PLL cells are negative for this indication. ATLL cells are TCL1 negative. They are positive for CD3, CD4, and CD25. They are CD7 negative; T-PLL cells are CD7 positive. By far, in ATLL, CD4 is more prevalent than CD8. Hypercalcemia is common in ATLL but NOT found in T-PLL. ATLL cells have a unique cytomorphology with "flower cells." These are cells having convoluted nuclei with condensed, homogeneous chromatin.
* T cell large granular lymphocyte leukemia (LGL): These cells are TCL1 negative but positive for CD2, CD3, CD8, CD16, and CD57. They variably express CD7 and rarely CD4. The patients may have mild-to-moderate splenomegaly but rarely lymphadenopathy. Cytopenias are a frequent finding. The cytology reveals large lymphocytes containing azurophilic granules. The median survival is over 10 years.
* Hairy cell leukemia (HCL); HCL is rare and is noted to be a low-grade mature B-cell cancer. 'Classic' HCL bears B-cell markers of CD19, CD20, and CD22. Markers more specific for this entity include CD11c, CD25, CD103, CD125, and CD200. An HCL variant exists that is missing both CD25 and CD123. CD22 and CD79b are variably expressed. However, the variant contains a characteristic BRAF-V600E mutation, a marker not evident in other B-cell maladies. The physical exam is noteworthy for massive splenomegaly, essentially its most prominent feature. Cellular morphology shows "hair"-like cytoplasmic projections. The variant form may manifest nucleoli.

**PROGNOSIS**

T-PLL is an aggressive malignancy with a median survival of 1 to 2 years. The median overall survival is 21 months. Some patients may present with the indolent variant, which shows a better prognosis. Poor prognostic factors include age above 65, effusion, hepatic or nervous system involvement, bulky lymph nodes, high absolute lymphocytic count, high expression of TCL1 and AKT1, and JAK3 mutation. Having at least 5 cytogenetic abnormalities was a negative prognostic factor for survival. An elevated LDH or beta-2-microglobulin reportedly portends a poor response to therapy.

**EPIDEMIOLOGY**

T-PLL is a rare T-cell leukemia. It accounts for approximately 2% of mature lymphocytic leukemia cases in adults. The pathology is common in elderly patients (older than 65 years) aged 30 to 94. There is a slight male predominance, with a male-to-female ratio of 1.33.

REFERENCE

<https://www.ncbi.nlm.nih.gov/books/NBK541000/#article-50561.s9>

### X-linked agammaglobulinemia

X-linked agammaglobulinemia (pronounced “ay-ga-muh-glaa-byou-luh-NEE-mee-uh”), or XLA, is a genetic condition where your body doesn’t make enough mature B-cells. B-cells are an important part of your immune system. They make proteins (antibodies) that help you fight off illnesses. People with XLA aren’t able to fight off illnesses easily and get sick often.

Because B-cells are important for developing certain immune system tissues, people with XLA often have underdeveloped or absent lymph nodes, tonsils and adenoids. Because of how you inherit it, it almost always affects males.

XLA is also called:

* Bruton’s agammaglobulinemia.
* Congenital agammaglobulinemia.
* Hypogammaglobulinemia.

Hypogammaglobulinemia is also a name used for common variable immunodeficiency (CVID), a condition similar to XLA. CVID is usually less severe and typically not diagnosed until adulthood. Providers typically diagnose people with XLA before the age of 1 or as young children.

#### X-linked agammaglobulinemia and severe combined immunodeficiency (SCID)

The difference between X-linked agammaglobulinemia and severe combined immunodeficiency (SCID) is that XLA affects your B-cells, and SCID affects your T-cells. Both are genetic conditions that affect your immune system and make you get sick frequently.

X-linked agammaglobulinemia is rare. It’s more common in males. Approximately 1 in 200,000 males are born with XLA.

## Symptoms and Causes

People with X-linked agammaglobulinemia usually have small or missing lymph nodes, tonsils and adenoids due to their underdeveloped immune systems. They experience frequent bacterial infections in childhood, including:

* Bronchitis.
* Ear infections (otitis media).
* Sinusitis.
* Pneumonia.
* Gastrointestinal infections.

Children with XLA usually aren’t more likely to get recurrent viral or fungal infections, like cytomegalovirus, RSV or the flu.

### What causes X-linked agammaglobulinemia?

XLA is a genetic illness you inherit from one or both biological parents. A change, or mutation, in your *BTK* gene causes it. This gene gives the instructions that tell your body how to make B-cells. B-cells make antibodies, an important part of your immune system that fights illness.

Changes in your *BTK* gene mean you can’t fight off illness the same way someone without the mutation can. This means you get sick frequently, sometimes with life-threatening illnesses.

#### What does X-linked mean?

We all get two sets of genes — one from each parent — in sets called chromosomes. Genes give our bodies instructions on how to make the proteins that keep our bodies working. Often, if there’s a change in one gene, having a second copy makes up for it, so your body can still function properly.

Males have mismatched sex chromosomes. They have one X and one Y. If one of these genes has a mutation, they don’t have another one to compensate for it. The BTK gene is on the X chromosome (X-linked). If they have a mutation in their BTK, they’ll have XLA.

Females have two X chromosomes. If they have one X chromosome with the mutation that causes XLA, they can still make enough mature B-cells because they have another functioning copy of BTK.

#### Risk factors for X-linked agammaglobulinemia

Having a family history of XLA is the only known risk factor.

#### Can girls have XLA?

Yes, it’s possible. But both parents would have to carry an X chromosome with the mutated *BTK* gene. Females can be carriers of the gene mutation and pass it on to their children, who might have XLA.

### Complications of XLA

Complications of X-linked agammaglobulinemia include:

* Chronic lung disease.
* Infections that spread to other parts of your body, like your blood or your brain.
* Possible increased risk of certain cancers.

## Diagnosis and Tests

A healthcare provider can perform blood tests to determine whether you or your child have XLA. If test results show a low level of B-cells or antibodies, they’ll do genetic testing to look for DNA changes.

## Management and Treatment

There’s no cure for XLA. But treatments can help you or your child avoid serious illness. They include:

* Replacement immunoglobulins (RIgG). Your healthcare provider gives you donor antibodies in a vein. You’ll need this treatment at least once per month.
* Proactive treatment of infections. Your provider will treat bacterial infections with antibiotics as soon as they think you’re sick.
* Avoiding live vaccinations. People with XLA can’t get live vaccines. These can make you sick or even be fatal. This includes the MMR, chickenpox (varicella) and oral polio vaccines.

## Outlook / Prognosis

People with XLA need treatment for the rest of their lives so they’re less vulnerable to illness. They’ll need to work closely with their healthcare provider to treat any illnesses as soon as possible. You or your child can expect to miss more days of school and work due to illness than others.

### How long do people with X-linked agammaglobulinemia live?

Thanks to advances in treatment, people with XLA live into adulthood in developed countries like the U.S. In still-developing countries, getting a diagnosis and treatment is much harder. This usually means children with XLA don’t live as long.

## Prevention

If you’re concerned about XLA, a healthcare provider can screen you for genetic conditions you could pass on to your child. If you’re a carrier of the mutation that causes XLA, you have a 50% chance of passing the mutation to a child. Any male children would have XLA. If you have XLA, your female children would be carriers. A genetic counselor or the provider who ordered the testing can advise you on your options if you’re a carrier or have XLA.

## Living With

The best way to take care of yourself with XLA is to prioritize your care. Keep appointments with your provider, and make sure you can recognize signs of an infection. Ask your provider what to do if you have symptoms of an infection.

### When should I see my healthcare provider?

Talk to a healthcare provider if:

* Your child gets sick from a live vaccine (this includes the MMR vaccine and chickenpox vaccine).
* Your child frequently gets sick with bacterial infections.
* You frequently get sick with bacterial infections.

A provider can tell you whether they need to look into it more.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for XLA is:

* Autosomal recessive agammaglobulinemia (ARA)
* Common variable immunodeficiency disease (CVID)
* Transient hypogammaglobulinemia of infancy (THI)
* X-linked hyper IgM syndrome (Hyper-IgM)
* X-linked lymphoproliferative disease (X-LPD)
* Severe combined immunodeficiency disease (SCID)

**EPIDEMIOLOGY**

XLA exclusively affects males. The reported incidence and prevalence of XLA vary considerably. Some sources report that XLA occurs at a rate of 1 in 190000 live births with a frequency of 1 per 100000 newborn males, and an estimated prevalence of 1 to 9 per 1000000. There is no known ethnic predisposition, but the reported incidence is highest in individuals of the White race.

Common aliases for X-linked agammaglobulinemia include Bruton agammaglobulinemia, Btk agammaglobulinemia, Bruton tyrosine kinase agammaglobulinemia, agammaglobulinemia of Bruton, and congenital agammaglobulinemia.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK549865/#article-31430.s10>

[X-Linked Agammaglobulinemia: Causes, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/24955-x-linked-agammaglobulinemia)

## Part 1

## Common Blood Disorders

Blood disorders disrupt the production or function of blood cells or clotting mechanisms, impacting overall health. Below is a detailed overview of the most prevalent blood disorders, including their definitions, symptoms, diagnostic methods, and treatment options.

### Anemia

**Definition and description**

Anemia occurs when the blood doesn't have enough hemoglobin or red blood cells.

This can happen if:

* The body doesn't make enough hemoglobin or red blood cells.
* Bleeding causes loss of red blood cells and hemoglobin faster than they can be replaced.
* The body destroys red blood cells and the hemoglobin that's in them.

**What red blood cells do**

The body makes three types of blood cells. White blood cells fight infection, platelets help blood clot and red blood cells carry oxygen throughout the body.

Red blood cells have an iron-rich protein that gives blood its red color, called hemoglobin. Hemoglobin let's red blood cells carry oxygen from the lungs to all parts of the body. And it let's red blood cells carry carbon dioxide from other parts of the body to the lungs to be breathed out.

Spongy matter inside many of the large bones, called bone marrow, makes red blood cells and hemoglobin. To make them, the body needs iron, vitamin B-12, folate and other nutrients from foods.

Anemia is characterized by a deficiency in the number or function of red blood cells, leading to reduced oxygen delivery to tissues. It is diagnosed when hemoglobin levels fall below 13.5 gm/dl in men or 12.0 gm/dl in women, with normal values for children varying by age

**Causes of anemia**

Different types of anemia have different causes. They include:

**Iron deficiency anemia.** Too little iron in the body causes this most common type of anemia. Bone marrow needs iron to make hemoglobin. Without enough iron, the body can't make enough hemoglobin for red blood cells.

Pregnant people can get this type of anemia if they don't take iron supplements. Blood loss also can cause it. Blood loss might be from heavy menstrual bleeding, an ulcer, cancer or regular use of some pain relievers, especially aspirin.

**Vitamin deficiency anemia.** Besides iron, the body needs folate and vitamin B-12 to make enough healthy red blood cells. A diet that doesn't have enough of these and other key nutrients can result in the body not making enough red blood cells.

Also, some people can't absorb vitamin B-12. This can lead to vitamin deficiency anemia, also called pernicious anemia.

**Anemia of inflammation.** Diseases that cause ongoing inflammation can keep the body from making enough red blood cells. Examples are cancer, HIV/AIDS, rheumatoid arthritis, kidney disease and Crohn's disease.

**Aplastic anemia.** This rare, life-threatening anemia occurs when the body doesn't make enough new blood cells. Causes of aplastic anemia include infections, certain medicines, autoimmune diseases and being in contact with toxic chemicals.

**Anemias linked to bone marrow disease.** Diseases such as leukemia and myelofibrosis can affect how the bone marrow makes blood. The effects of these types of diseases range from mild to life-threatening.

**Hemolytic anemias.** This group of anemias is from red blood cells being destroyed faster than bone marrow can replace them. Certain blood diseases increase how fast red blood cells are destroyed. Some types of hemolytic anemia can be passed through families, which is called inherited.

**Sickle cell anemia.** This inherited and sometimes serious condition is a type of hemolytic anemia. An unusual hemoglobin forces red blood cells into an unusual crescent shape, called a sickle. These irregular blood cells die too soon. That causes an ongoing shortage of red blood cells.

**Risk factors of anemia**

These factors can increase risk of anemia:

* **A diet that doesn't have enough vitamins and minerals.** Not getting enough iron, vitamin B-12 and folate increases the risk of anemia.
* **Problems with the small intestine.** Having a condition that affects how the small intestine takes in nutrients increases the risk of anemia. Examples are Crohn's disease and celiac disease.
* **Menstrual periods.** In general, having heavy periods can create a risk of anemia. Having periods causes the loss of red blood cells.
* **Pregnancy.** Pregnant people who don't take a multivitamin with folic acid and iron are at an increased risk of anemia.
* **Ongoing, called chronic, conditions.** Having cancer, kidney failure, diabetes or another chronic condition increases the risk of anemia of chronic disease. These conditions can lead to having too few red blood cells.
* Slow, chronic blood loss from an ulcer or other source within the body can use up the body's store of iron, leading to iron deficiency anemia.
* **Family history.** Having a family member with a type of anemia passed through families, called inherited, can increase the risk of inherited anemias, such as sickle cell anemia.
* **Other factors.** A history of certain infections, blood diseases and autoimmune conditions increases the risk of anemia. Drinking too much alcohol, being around toxic chemicals, and taking some medicines can affect the making of red blood cells and lead to anemia.
* **Age.** People over age 65 are at increased risk of anemia.

**Symptoms of anemia**

Anemia symptoms depend on the cause and how bad the anemia is. Anemia can be so mild that it causes no symptoms at first. But symptoms usually then occur and get worse as the anemia gets worse.

If another disease causes the anemia, the disease can mask the anemia symptoms. Then a test for another condition might find the anemia. Certain types of anemia have symptoms that point to the cause.

Possible symptoms of anemia include:

Tiredness.

* Weakness.
* Shortness of breath.
* Pale or yellowish skin, which might be more obvious on white skin than on Black or brown skin.
* Irregular heartbeat.
* Dizziness or lightheadedness.
* Chest pain.
* Cold hands and feet.
* Headaches.

**Diagnosis and Test**

A blood test measuring hemoglobin levels is the primary diagnostic tool. Additional tests, such as a complete blood count (CBC) or iron studies, help identify the underlying cause.

To diagnose anemia, your health care provider is likely to ask you about your medical and family history, do a physical exam, and order blood tests. Tests might include:

* **Complete blood count (CBC).** A CBC is used to count the number of blood cells in a sample of blood. For anemia, the test measures the amount of the red blood cells in the blood, called hematocrit, and the level of hemoglobin in the blood.
* Typical adult hemoglobin values are generally 14 to 18 grams per deciliter for men and 12 to 16 grams per deciliter for women. Typical adult hematocrit values vary among medical practices. But they're generally between 40% and 52% for men and 35% and 47% for women.
* **A test to show the size and shape of the red blood cells.** This looks at the size, shape and color of the red blood cells.

**Other diagnostic tests**

If you get a diagnosis of anemia, you might need more tests to find the cause. Sometimes, it can be necessary to study a sample of bone marrow to diagnose anemia.

**Treatment**

Anemia treatment depends on the cause.

**Iron deficiency anemia.** Treatment for this form of anemia usually involves taking iron supplements and changing the diet.

If the cause of iron deficiency is loss of blood, finding the source of the bleeding and stopping it is needed. This might involve surgery.

**Vitamin deficiency anemias.** Treatment for folic acid and vitamin B-12 deficiency involves dietary supplements and increasing these nutrients in the diet.

People who have trouble absorbing vitamin B-12 from food might need vitamin B-12 shots. First, the shots are every other day. In time, the shots will be shots just once a month, possibly for life.

**Anemia of chronic disease.** Treatment for this type of anemia focuses on the disease that's causing it. If symptoms become severe, treatment might include getting blood, called a transfusion, or shots of a hormone called erythropoietin.

**Anemias associated with bone marrow disease.** Treatment of these various diseases can include medicines, chemotherapy or getting bone marrow from a donor, called a transplant.

**Aplastic anemia.** Treatment for this anemia can include blood transfusions to boost levels of red blood cells. A bone marrow transplant might be needed if bone marrow can't make healthy blood cells.

**Hemolytic anemias.** Managing hemolytic anemias includes stopping medicines that might be causing it and treating infections. If the immune system is attacking red blood cells, treatment might involve taking medicines that lower immune system activity.

**Sickle cell anemia.** Treatment might include oxygen, pain relievers, and hydration with fluids given through a vein, called intravenous, to reduce pain and prevent complications. Receiving blood, called a transfusion, and taking folic acid supplements and antibiotics might be involved.

A cancer drug called hydroxyurea (Droxia, Hydrea, Siklos) also is used to treat sickle cell anemia.

**Thalassemia.** Most forms of thalassemia are mild and need no treatment. More-severe forms of thalassemia generally require blood transfusions, folic acid supplements, medicines, a blood and bone marrow stem cell transplant, or, rarely, removing the spleen.

**Complications of anemia**

If not treated, anemia can cause many health problems, such as:

* **Severe tiredness.** Severe anemia can make it impossible to do everyday tasks.
* **Pregnancy complications.** Pregnant people with folate deficiency anemia may be more likely to have complications, such as premature birth.
* **Heart problems.** Anemia can lead to a rapid or irregular heartbeat, called arrhythmia. With anemia, the heart must pump more blood to make up for too little oxygen in the blood. This can lead to an enlarged heart or heart failure.
* **Death.** Some inherited anemias, such as sickle cell anemia, can lead to life-threatening complications. Losing a lot of blood quickly causes severe anemia and can be fatal.

**Prevention of anemia**

Many types of anemia can't be prevented. But eating a healthy diet might prevent iron deficiency anemia and vitamin deficiency anemias. A healthy diet includes:

* **Iron.** Iron-rich foods include beef and other meats, beans, lentils, iron-fortified cereals, dark green leafy vegetables, and dried fruit.
* **Folate.** This nutrient, and its human-made form folic acid, can be found in fruits and fruit juices, dark green leafy vegetables, green peas, kidney beans, peanuts, and enriched grain products, such as bread, cereal, pasta and rice.
* **Vitamin B-12.** Foods rich in vitamin B-12 include meat, dairy products, and fortified cereals and soy products.
* **Vitamin C.** Foods rich in vitamin C include citrus fruits and juices, peppers, broccoli, tomatoes, melons, and strawberries. These also help the body take in iron.

If you're concerned about getting enough vitamins and minerals from food, ask your health care provider about taking a multivitamin.

**Prognosis/ outlook**

Most cases are manageable with treatment, though severe forms like aplastic anemia may require ongoing care.

**Epidemiology**

The mean age of respondents was 35±11.8 years, with 28.9% of respondents being anemic. Female respondents (52.7%) were more than male respondents (47.3%). Female respondents (39.2%) had a higher prevalence of anemia than male respondents (17.5%). There was a significant association between sex, level of education, and anemia status. Being female, having no formal education, or only having a primary school level of education were significant predictors of anemia [odds ratio (OR)=2.55; 95% confidence interval (CI)=1.54, 4.23; P=0.00; OR=12.57; 95%CI=2.39, 66.27; P=0.00; and OR=2.54; 95%CI=1.16, 5.58; P=0.02 respectively.

### There was a higher prevalence of anemia among women, younger people, and those with no or only primary levels of formal education. Awareness programs targeted at women and people with lower levels of education are necessary to reduce the overall prevalence of anemia in this region.

Anemia is a significant health issue in Nigeria, affecting various demographics. According to recent studies, the prevalence of anemia in Nigeria is as follows: children under 5 years old have a 71% prevalence rate, non-pregnant women aged 15-49 years have a 47.3% rate, and pregnant women have a 57.5% rate.

In Lagos, Southwest Nigeria, a study found that the overall prevalence of anemia among adults is high, with factors such as sex, education level, and wealth quintiles significantly associated with the condition.

Females are more likely to be anemic compared to males, and individuals with lower educational attainment and those in the lowest wealth quintiles have a higher risk of anemia.

The study also highlighted dietary factors as important contributors to anemia. For instance, the frequency of consumption of red meat, chicken, fish, legumes, and green leafy vegetables was associated with anemia, although not all associations reached statistical significance.

Nigeria is listed by the WHO as one of the countries with a severe burden of anemia, with over 40% of the population affected.

This high prevalence can contribute to the depletion of already strained resources and increase the overall burden of disease in less developed countries.

In conclusion, anemia is a major public health concern in Nigeria, particularly affecting children and women, and is influenced by various socioeconomic and dietary factors.

Prevalence in Children: 71% of children under 5 years old are anemic.

Prevalence in Non-Pregnant Women: 47.3% of non-pregnant women aged 15-49 years are anemic.

Prevalence in Pregnant Women: 57.5% of pregnant women are anemic.

Factors Associated with Anemia: Sex, education level, and wealth quintiles are significantly associated with anemia.

Dietary Factors: Consumption of red meat, chicken, fish, legumes, and green leafy vegetables is associated with anemia.

## Differential Diagnoses

* Alpha Thalassemia
* Aplastic Anemia
* Beta Thalassemia
* Hemolytic Anemia
* Iron Deficiency Anemia
* Low LDL Cholesterol (Hypobetalipoproteinemia)
* Megaloblastic Anemia
* Myelophthisic Anemia
* Pernicious Anemia
* Sickle Cell Disease (SCD)
* Spur Cell Anemia

## 

## When to see a doctor

Some people learn that their hemoglobin is low when they try to donate blood. Being turned down for blood donation isn't necessarily a cause for concern. You can have a hemoglobin count that's fine for you but doesn't meet the standards blood donation centers set.

If your hemoglobin count is only a little under the required level, particularly if you've been accepted for blood donation in the past, you might just need to wait a couple of months and try again. If the problem continues, make an appointment with your healthcare professional.

### Make an appointment if you have symptoms

If you have symptoms of a low hemoglobin count, make an appointment with your healthcare team. Symptoms can include:

* Fatigue
* Pale skin and gums
* Shortness of breath
* A fast or irregular heartbeat

Your healthcare team might recommend a complete blood count test to determine whether you have a low hemoglobin count. If your test reveals that you have a low hemoglobin count, you'll likely need more testing to determine the cause.

**Reference**

[**Low hemoglobin count When to see a doctor - Mayo Clinic**](https://www.mayoclinic.org/symptoms/low-hemoglobin/basics/when-to-see-doctor/sym-20050760)

<https://www.mayoclinic.org/diseases-conditions/anemia/diagnosis-treatment/drc-20351366>

https://pmc.ncbi.nlm.nih.gov/articles/PMC10280247/

### Sickle Cell Disease

**Definition and Description**

Sickle cell disease is an inherited disorder where abnormal hemoglobin causes red blood cells to become rigid and sickle-shaped, leading to blockages in blood vessels and complications like stroke or organ damage. It affects approximately 70,000 to 100,000 Americans

Sickle cell disease (SCD) is a group of inherited red blood cell disorders. Red blood cells contain hemoglobin, a protein that carries oxygen. Healthy red blood cells are round, and they move through small blood vessels to carry oxygen to all parts of the body.

In someone who has SCD, the hemoglobin is abnormal, which causes the red blood cells to become hard and sticky and look like a C-shaped farm tool called a sickle. The sickle cells die early, which causes a constant shortage of red blood cells. Also, when they travel through small blood vessels, sickle cells get stuck and clog the blood flow. This can cause pain and other serious complications (health problems) such as infection, acute chest syndrome, and stroke.

## Types of sickle cell disease

## There are several types of SCD. The specific type of SCD a person has depends on the genes they inherited from their parents. People with SCD inherit genes that contain instructions, or code, for abnormal hemoglobin.

Below are the most common types of SCD:

### HbSS­­­­

People who have this form of SCD inherit two genes, one from each parent, that code for hemoglobin "S." Hemoglobin S is an abnormal form of hemoglobin that causes the red cells to become rigid, and sickle shaped. This is commonly called sickle cell anemia and is usually the most severe form of the disease.

### HbSC

People who have this form of SCD inherit a hemoglobin S gene from one parent and a gene for a different type of abnormal hemoglobin called "C" from the other parent. This is usually a milder form of SCD.

### HbS beta thalassemia

People who have this form of SCD inherit a hemoglobin S gene from one parent and a gene for beta thalassemia, another type of hemoglobin abnormality, from the other parent. There are two types of beta thalassemia: "zero" (HbS beta0) and "plus" (HbS beta+). Those with HbS beta0-thalassemia usually have a severe form of SCD. People with HbS beta+-thalassemia tend to have a milder form of SCD.

There also are a few rare types of SCD, such as the following:

### HbSD, HbSE, and HbSO

People who have these forms of SCD inherit one hemoglobin S gene and one gene that codes for other abnormal types of hemoglobin ("D," "E," or "O"). The severity of these rarer types of SCD varies.

## What causes sickle cell disease?

SCD is an inherited disease caused by a defect in a gene:

You are born with SCD only if 2 genes are inherited—1 from each parent.

If you have just 1 gene you are healthy, but you are a carrier of the disease. If 2 carriers have a child, there is a greater chance their child will have SCD.

Parents who are each a carrier of a sickle cell gene have a 1 in 4 chance of having a child with SCD.

## Who is at risk for sickle cell disease?

Having a family history of SCD increases your risk for the disease. SCD mainly affects people whose families came from Africa, Central America, South America, the Middle East, Asia, India, the Mediterranean, or Southern Europe. One in 365 Black babies in the U.S. is born with SCD. One in 13 Black babies in the U.S. carries the sickle cell gene.

## symptoms of sickle cell disease

Each person’s symptoms may vary. They may be mild or severe. Symptoms may include: Having fewer red blood cells causes anemia. Severe anemia can make you feel dizzy, short of breath, and tired.

**Yellowing of the skin, eyes, and mouth (jaundice).** This symptom is common. Sickle cells don’t live as long as normal red blood cells. They die faster than the liver can filter them out. The yellow color is caused by a substance (bilirubin) that is released when the red blood cells die.

**Pain crisis, or sickle crisis.** When sickle cells move through small blood vessels, they can get stuck. They can block blood flow and cause pain. The sudden pain can occur anywhere. But it most often happens in the chest, arms, and legs. Blocked blood flow may also cause tissue death.

**Acute chest syndrome.** This condition occurs when sickle cells stick together and block oxygen flow in the tiny vessels in the lungs. It can be life-threatening. It often happens suddenly when the body is under stress from infection, fever, or dehydration. Symptoms may seem like pneumonia. They can include fever, pain, and a violent cough.

**Splenic sequestration (pooling).** The spleen becomes enlarged and painful when sickle cells get stuck there. Fewer red blood cells are able to move, causing a sudden drop in hemoglobin. It can be deadly if not treated at once.

**Stroke.** A stroke is another sudden and severe problem that occurs with this disease. The sickle cells can block the major blood vessels that bring oxygen to the brain. Any interruption in the flow of blood and oxygen to the brain can cause severe brain damage. If you have a stroke from SCD, you are more likely to have a second and third stroke.

**Priapism.** The sickle cells block the blood vessels in the penis, causing great pain. If not treated right away, it can cause erectile dysfunction.

The symptoms of SCD may look like other blood disorders or health problems. Always see your healthcare provider for a diagnosis.

**Diagnosis and Test**

Newborn screening is standard in the United States, allowing early detection. Prenatal diagnosis is possible through amniotic fluid or placental tissue testing.

Your healthcare provider will take your health history and give you a physical exam. You may also have blood tests and other tests.

Many states routinely screen newborns for SCD. Treatment can then begin as soon as possible. Early diagnosis and treatment can reduce the risk of problems.

A blood test called hemoglobin electrophoresis may be done. It can tell if you are a carrier of SCD. It can also tell if you have any of the diseases linked with the sickle cell gene.

**Treatment**

Treatment will depend on your symptoms, age, and general health. It will also depend on how severe the condition is.

Early diagnosis and preventing further problems is critical in treating SCD. Treatment goals include preventing organ damage (including strokes), preventing infection, and treating symptoms. Treatment may include:

* Pain medicines. These are used for sickle cell crises.
* Drinking plenty of water daily (8 to 10 glasses). Doing so can prevent and treat pain crises. In some cases, IV (intravenous) fluids may be needed.
* Blood transfusions. These may help treat anemia and prevent stroke. They are also used to dilute the sickled hemoglobin with normal hemoglobin. It is done to treat chronic pain, acute chest syndrome, splenic sequestration, and other emergencies.
* Red blood cell exchange.This process removes some abnormal red blood cells and replaces them with healthy red blood cells from a donor. This can help improve symptoms.
* Vaccines and antibiotics. These are used to prevent infections.
* Folic acid. This B vitamin helps prevent severe anemia.
* Hydroxyurea. This medicine helps reduce the frequency of pain crises and acute chest syndrome. It may also help decrease the need for blood transfusions.
* Voxelotor. This medicine is approved for people age 4 and older to reduce pain crises and improve anemia caused by red blood cell destruction.
* Crizanlizumab. This medicine is approved for people age 16 and older to reduce pain crises.
* L-glutamine. This medicine is approved for people age 5 and older to reduce pain crises.
* Regular eye exams. These are done to screen for an eye condition called retinopathy.
* Bone marrow transplant. A transplant can cure some people with SCD. The decision to have a transplant is based on the severity of the disease and finding a suitable donor. These decisions need to be discussed with your provider. Transplants are done only at specialized medical centers.
* Gene therapyNew gene therapies have been approved to treat SCD. Talk with your provider (or your child's provider) about these treatments.

## possible complications

SCD can affect any major organ. The liver, heart, kidneys, gallbladder, eyes, bones, and joints can all be damaged. They suffer damage from the abnormal function of the sickle cells and their inability to flow through the small blood vessels correctly. Problems may include :

* Increased infections and fever
* Leg ulcers or serious sores
* Bone tissue damage or death
* Early gallstones
* Kidney damage and loss of body water in the urine
* Eye damage
* Multiple organ failure
* Acute chest syndrome causing lung damage. This is a medical emergency.
* Anemia
* Blood clots
* Painful swelling of hands and feet

## Living with sickle cell disease

SCD is an ongoing (chronic) condition. You may not be able to fully prevent the complications of this disease but living a healthy lifestyle may reduce some of the problems. This includes doing things such as:

* Eating a healthy diet with lots of fruits, vegetables, whole grains, and protein
* Getting enough sleep
* Drinking lots of fluids

Stay away from things that may trigger a crisis, such as:

* High altitudes
* Cold weather or sudden changes in temperature
* Swimming in cold water
* Heavy physical labor
* Medicines for nasal congestion (decongestants). They cause blood vessels to narrow (constrict).
* Stress or exhaustion
* Alcohol
* Smoking

Prevent infections by:

* Getting vaccines as recommended by your healthcare provider
* Washing your hands often
* Staying away from people who are sick
* Getting regular dental exams
* Following food safety guidelines when cooking, eating, and preparing foods

**Prognosis**

With proper management, patients can live into adulthood, but complications may reduce life expectancy.

### What can I expect if I have sickle cell disease?

People with sickle cell disease have a reduced life expectancy. New treatments for SCD are improving life expectancy and quality of life. People with sickle cell disease can survive beyond their 50s with optimal management of the disease.

## If your child has sickle cell disease, there are many things you can do to help manage their condition:

* Take your child to see their healthcare provider regularly.
* Make sure your child gets all their recommended vaccines.
* Help your child get regular exercise and eat a heart-healthy diet.
* During a pain crisis, have your child drink lots of fluids and take a nonsteroidal anti-inflammatory drug (NSAID).
* If you can’t manage their pain at home, take them to the hospital for stronger pain medication.

## Differential Diagnosis

## The differential diagnosis of sickle cell disease includes other conditions that may present with fatigue, infection, bone pain, such as:

* Thalassemia
* Acute leukemia
* Autoimmune hemolytic anemia
* HbSC disease
* HbS-beta-thalassemia
* Septic arthritis
* Polycythemia vera
* Systemic lupus erythematosus
* Other hemoglobinopathies

**When to see a doctor**

Newborns who test positive for hemoglobin S (HbS) are tested again after 2 months to get a more accurate diagnosis of their specific SCD type. The family can then receive education before symptoms appear and begin penicillin and immunizations as needed.

### Sickle cell trait

Screening can also identify infants who are carriers of SCD, called sickle cell trait. This may not be immediately helpful to infants with sickle cell trait because they usually do not show symptoms. However, the infant’s parents should be offered education and testing because it could affect future reproductive decisions.

**Epidemiology**

It's estimated that 25 million individuals live with the genetic blood disorder. Globally, the majority of individuals with sickle cell disease live in sub-Saharan Africa, and more specifically, Nigeria carries the highest burden of disease where sickle cell trait (SCT) is present in 25% of the population.

According to an assessment of Nigerian healthcare policies and practices, to mitigate this burden, many churches require hemoglobin electrophoresis tests for couples who intend to marry, as an attempt to reduce the prevalence of sickle cell disease. Despite controversy, churches continue to implement the practice.

"Considering the burden of sickle cell disease in the Nigerian setting, it is of critical importance to explore the views and experiences of this category of stakeholders,"

The geographic distribution of the sickle-cell trait is very similar to that of malaria. The sickle cell trait has a partial protective effect against malaria, and this may explain why it has been maintained at such high prevalence levels in tropical Africa. Those who inherit the gene from both parents do not have this protection. In addition, they suffer from severe effects of sickle-cell disease and many die before they reach reproductive age. In some countries where sickle-cell disease is a major public health concern, control programmes do exist; however, these have neither the national coverage nor basic facilities to manage patients. Systematic screening for sickle-cell disease using a simple blood test is not a common practice, and diagnosis is usually made when a severe complication occurs. Counselling and prevention of causes and infections are simple measures not readily accessible to most patients. As a result, the majority of children with the most severe form of the disease die before the age of five, usually from an infection or severe anaemia. The survivors remain vulnerable to exacerbations of the disease and the complications mentioned above.

Sickle-cell disease has major social and economic implications for the affected child as well as the family. Recurrent sickle-cell crises interfere with the patient’s life, especially with regard to education, work and psychosocial development. Presently, there is no cure for sickle-cell disease. However, cost-effective treatment exists for the pain and other aspects of the disease.

The most important components of this treatment are early intervention with analgesics, antibiotics, rest, good nutrition, folic acid supplementation and high fluid intake. At times, invasive procedures such as blood transfusions and surgery may be needed.

Research in some countries in the Region (Benin, Burkina Faso, Nigeria, Togo) has yielded therapeutic agents effective in preventing or reducing the frequency and severity of crises.. There is sufficient evidence that neonatal screening for sickle-cell disease, when linked to timely diagnostic testing, parental education and comprehensive care, markedly reduces morbidity and mortality in infancy and early childhood. Nevertheless, simple, inexpensive and cost-effective procedures such as the use of penicillin to prevent infections are not available to most patients.

**Reference**

[How is Sickle Cell Disease Diagnosed?](https://sickle-cell.com/diagnosis)

<https://www.cdc.gov/sickle-cell/about/index.html>

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/sickle-cell-disease>

<https://my.clevelandclinic.org/health/diseases/12100-sickle-cell-disease>

<https://www.afro.who.int/sites/default/files/2017-06/AFR-RC56-17%20Sickle%20Cell%20Disease%20-%20Final.pdf>

### Hemophilia

**Definition and description**

Hemophilia is a genetic bleeding disorder caused by deficient or defective clotting factors (factor VIII in hemophilia A, factor IX in hemophilia B), resulting in prolonged bleeding

## Hemophilia is a rare disorder in which the blood doesn't clot in the typical way because it doesn't have enough blood-clotting proteins (clotting factors). If you have hemophilia, you might bleed for a longer time after an injury than you would if your blood clotted properly.

Small cuts usually aren't much of a problem. If you have a severe form of the condition, the main concern is bleeding inside your body, especially in your knees, ankles and elbows. Internal bleeding can damage your organs and tissues and be life-threatening.

Hemophilia is almost always a genetic disorder. Treatment includes regular replacement of the specific clotting factor that is reduced. Newer therapies that don't contain clotting factors also are being used.

**Causes of hemophilia**

When a person bleeds, the body typically pools blood cells together to form a clot to stop the bleeding. Clotting factors are proteins in the blood that work with cells known as platelets to form clots. Hemophilia occurs when a clotting factor is missing or levels of the clotting factor are low.

### Congenital hemophilia

Hemophilia is usually inherited, meaning a person is born with the disorder (congenital). Congenital hemophilia is classified by the type of clotting factor that's low.

The most common type is hemophilia A, associated with a low level of factor 8 The next most common type is hemophilia B, associated with a low level of factor 9.

### Acquired hemophilia

Some people develop hemophilia with no family history of the disorder. This is called acquired hemophilia.

Acquired hemophilia is a variety of the condition that occurs when a person's immune system attacks clotting factor 8 or 9 in the blood. It can be associated with:

* Pregnancy
* Autoimmune conditions
* Cancer
* Multiple sclerosis
* Drug reactions

### Hemophilia inheritance

In the most common types of hemophilia, the faulty gene is located on the X chromosome. Everyone has two sex chromosomes, one from each parent. Females inherit an X chromosome from the mother and an X chromosome from the father. Males inherit an X chromosome from the mother and a Y chromosome from the father.

This means that hemophilia almost always occurs in boys and is passed from mother to son through one of the mother's genes. Most women with the defective gene are carriers who have no signs or symptoms of hemophilia. But some carriers can have bleeding symptoms if their clotting factors are moderately decreased.

**Risk factors of hemophilia**

The biggest risk factor for hemophilia is to have family members who also have the disorder. Males are much more likely to have hemophilia than are females.

**Symptoms of hemophilia**

Signs and symptoms of hemophilia vary, depending on your level of clotting factors. If your clotting-factor level is mildly reduced, you might bleed only after surgery or trauma. If your deficiency is severe, you can bleed easily for seemingly no reason.

Signs and symptoms of spontaneous bleeding include:

* Unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work
* Many large or deep bruises
* Unusual bleeding after vaccinations
* Pain, swelling or tightness in your joints
* Blood in your urine or stool
* Nosebleeds without a known cause
* In infants, unexplained irritability

### Bleeding into the brain

A simple bump on the head can cause bleeding into the brain for some people who have severe hemophilia. This rarely happens, but it's one of the most serious complications that can occur. Signs and symptoms include:

* Painful, prolonged headache
* Repeated vomiting
* Sleepiness or lethargy
* Double vision
* Sudden weakness or clumsiness
* Convulsions or seizures

Easy bruising, bleeding gums, heavy bleeding from minor cuts, frequent nosebleeds, heavy menstrual bleeding, joint bleeding, and excessive bleeding post-surgery.

## 

## Diagnosis and Test

Severe cases of hemophilia usually are diagnosed within the first year of life. Mild forms might not be apparent until adulthood. Some people learn they have hemophilia after they bleed excessively during a surgical procedure.

Clotting-factor tests can reveal a clotting-factor deficiency and determine how severe the hemophilia is.

For people with a family history of hemophilia, genetic testing might be used to identify carriers to make informed decisions about becoming pregnant.

It's also possible to determine during pregnancy if the fetus is affected by hemophilia. However, the testing poses some risks to the fetus. Discuss the benefits and risks of testing with your doctor.

Blood tests measure clotting factor levels to confirm the diagnosis and determine the type and severity.

**Treatment**

The main treatment for severe hemophilia involves replacing the clotting factor you need through a tube in a vein.

This replacement therapy can be given to treat a bleeding episode in progress. It can also be given on a regular schedule at home to help prevent bleeding episodes. Some people receive continuous replacement therapy.

Replacement clotting factors can be made from donated blood. Similar products, called recombinant clotting factors, are made in a laboratory, not from human blood.

Other therapies include:

* **Desmopressin.** In some forms of mild hemophilia, this hormone can stimulate the body to release more clotting factors. It can be injected slowly into a vein or used as a nasal spray.
* **Emicizumab (Hemlibra).** This is a newer drug that doesn't include clotting factors. This drug can help prevent bleeding episodes in people with hemophilia A.
* **Clot-preserving medications.** Also known as anti-fibrinolytics, these medications help prevent clots from breaking down.
* **Fibrin sealants.** These can be applied directly to wound sites to promote clotting and healing. Fibrin sealants are especially useful for dental work.
* **Physical therapy.** It can ease signs and symptoms if internal bleeding has damaged your joints. Severe damage might require surgery.
* **First aid for minor cuts.** Using pressure and a bandage will generally take care of the bleeding. For small areas of bleeding beneath the skin, use an ice pack. Ice pops can be used to slow down minor bleeding in the mouth.
  + Regular infusions of synthetic or donor-derived clotting factors.
  + Avoiding medications like aspirin that impair clotting.
  + Physical therapy to manage joint damage from repeated bleeding.

**Complications of hemophilia**

Complications of hemophilia can include:

* Deep internal bleeding. Bleeding that occurs in deep muscle can cause the limbs to swell. The swelling can press on nerves and lead to numbness or pain. Depending on where the bleeding occurs, it could be life-threatening.
* Bleeding into the throat or neck. This can affect a person's ability to breathe.
* Damage to joints. Internal bleeding can put pressure on the joints, causing severe pain. Left untreated, frequent internal bleeding can cause arthritis or destruction of the joint.
* Infection. If the clotting factors used to treat hemophilia come from human blood, there's an increased risk of viral infections such as hepatitis C. Because of donor screening techniques, the risk is low.
* Adverse reaction to clotting factor treatment. In some people with severe hemophilia, the immune system has a negative reaction to the clotting factors used to treat bleeding. When this happens, the immune system develops proteins that keep the clotting factors from working, making treatment less effective.

**Prognosis**

With modern treatments, patients can lead normal lives, though joint damage may occur over time.

Hemophilia is chronic. People with the condition need treatment throughout their lives. The type and frequency of treatment depend on factors such as the type of hemophilia and its severity.

Life expectancy also varies in people with hemophilia. In the past, people with hemophilia rarely lived past adolescence. However, today, people with hemophilia who receive appropriate treatment generally lead full lives.

On average, hemophilia is still associated with a shorter life expectancy, but lifespan is increasing as treatments continue to improve.

**prevention of hemophilia**

* Get an annual checkup at a Hemophilia Treatment Center (HTC)
* Get your hepatitis A and hepatitis B vaccines
* Proper route of vaccine administration
* Have an emergency plan for severe bleeding
* Indulge in physical activities and exercise
* Get tested regularly for blood-borne infections
* Protect your kids from hemophilia
* Maintain good oral health

## Lifestyle and home remedies

To avoid excessive bleeding and protect your joints:

* **Exercise regularly.** Activities such as swimming, bicycle riding and walking can build muscles while protecting joints. Contact sports — such as football, hockey or wrestling — are not safe for people with hemophilia.
* **Avoid certain pain medications.** Drugs that can make bleeding worse include aspirin and ibuprofen (Advil, Motrin IB, others). Instead, use acetaminophen (Tylenol, others), which is a safer alternative for mild pain relief.
* **Avoid blood-thinning medications.** Medications that prevent blood from clotting include heparin, warfarin (Jantoven), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa) and dabigatran (Pradaxa).
* **Practice good dental hygiene.** The goal is to prevent tooth and gum disease, which can lead to excessive bleeding.
* **Get vaccinations.** People with hemophilia should receive recommended vaccinations at the appropriate ages, as well as hepatitis A and B. Requesting use of the smallest gauge needle and having pressure or ice applied for 3 to 5 minutes after the injection can reduce the risk of bleeding.
* **Protect your child from injuries that could cause bleeding.** Knee Pads, elbow pads, helmets and safety belts all help prevent injuries from falls and other accidents. Keep your home free of furniture with sharp corners.

**Epidemiology**

Hemophilia affects patients worldwide. A global report from the World Federation of Hemophilia found that 67% of cases occur in low- and lower-middle-income countries. The study also found that hemophilia can negatively impact employment, with 12% of patients reporting that hemophilia led them to part-time work, extended leave, or unemployment.Most people with hemophilia report mobility problems, pain, and bleeding incidents.

Healthcare costs for people with hemophilia can also be significant. In the United States, the average price tag for managing hemophilia B is greater than $200,000 per patient annually, with the cost exceeding $630,000 for patients with severe hemophilia B.

In Europe, the average annual per-patient cost of severe hemophilia A and B is about €200,000, according to a study that examined costs in France, Germany, Italy, Spain, and the United Kingdom. Drugs accounted for almost 98% of direct costs. In Australia, the average annual per-patient cost for moderate to severe hemophilia A is about €74,000

**when to see a doctor**

### Head or Neck Bleeding

If your child has any of the following symptoms, he should see a doctor right away. These could be signs of bleeding inside the head:

* Headache with vomiting
* Severe headache
* Blurred vision
* Sleeping a lot
* Personality change or child's mood is different
* Seizures

A child who gives himself a factor at home should immediately give himself one dose of factor after a head injury. Then he should see the doctor.

### Abdominal Bleeding

If your child has any of these symptoms of abdominal bleeding, call the doctor:

* Severe abdominal (stomach) pain with no explained cause
* Severe back pain
* Blood in the urine or stool

### Joint Bleeding

If your child has any of these complaints, he may have bleeding into a joint and will need a clotting factor. Call the doctor right away.

* Tingling or "bubbling" feeling in a joint
* Stiffness and pain in a joint
* Swollen, tender, warm and painful joint
* Limited or painful movement of the joint

### Soft Tissue or Muscle Bleeding

If your child has any of these signs of soft tissue or muscle bleeding, call the doctor:

* A raised bump
* Pain, swelling; area is warm to the touch
* Trouble using the injured area

### Mouth Bleeding

If your child has bleeding from the lips, gums or tongue, apply pressure and ice packs. If the bleeding does not stop, call the hemophilia team. Do not let him eat or suck a pacifier. Continue to hold ice packs over the cut until your child has been treated or until bleeding has stopped.

### Cuts and Scrapes

* Apply pressure over the cut for 5 to 10 minutes.
* If the bleeding does not stop in 10 minutes, your child probably needs a clotting factor.
* If you think the cut needs stitches, take your child to the doctor.

Remember: Before your child gets stitches, he MUST be treated with a clotting factor.

## Differential Diagnosis

## Other conditions can also present similarly with bleeding after minor trauma or spontaneous bleeds and require exclusion before confirming the diagnosis of hemophilia.

## Some of these conditions include von Willebrand disease, scurvy, diseases of platelet dysfunction, deficiency of other coagulation factors like V, VII, X, or fibrinogen, Ehlers-Danlos syndrome, Fabry disease, disseminated intravascular coagulation, and child abuse.

## In von Willebrand disease, bleeding symptoms can be similar to mild hemophilia, but patients with von Willebrand disease have more mucosal bleeding compared to musculoskeletal bleeding seen in hemophilia.

## Von Willebrand disease is diagnosed by checking for von Willebrand factor antigen or von Willebrand factor multimers.

## Similarly, in scurvy, Ehlers-Danlos syndrome, and Fabry disease; also, the bleeding is usually mucosal, unlike hemophilia, where it is musculoskeletal. In scurvy, there is a deficiency of vitamin C.

## In Ehlers-Danlos syndrome, the skin is hyperextensible, and joints are hypermobile. The diagnosis is usually through clinical features, genetic testing, and tissue biopsy. Similarly, in Fabry disease, patients may also have other organs being affected, including kidneys and heart, and have skin lesions called angiokeratomas. They also have pain in the extremities.

## Fabry disease is usually diagnosed with clinical findings and genetic testing. In cases of platelet dysfunction disorders, bleeding is usually mucocutaneous, unlike hemophilia. Usually, these disorders are diagnosed by platelet aggregation studies or platelet electron microscopy. In the deficiency of other coagulation factors, musculoskeletal bleeding is uncommon.

## In fact, sometimes thrombosis can occur, especially in patients with factor VII or fibrinogen deficiency or in patients with combined factor V and VIII deficiency. Specific coagulation factor assays usually confirm the diagnosis. Disseminated intravascular coagulation (DIC) that mimics hemophilia is hard to differentiate, but usually, there is an underlying condition in DIC, for example, acute promyelocytic leukemia. Diagnosis is usually carried out by blood tests that show decreased platelet count and the absence of factor VIII autoantibodies. Child abuse can sometimes be misidentified and confused with hemophilia, and it is essential to find inconsistencies in the history of how trauma has occurred. Other signs of malnourishment require vigilance, and X-rays may reveal evidence of fractures of different ages.

## Reference

## https://www.pfizer.com/disease-and-conditions/hemophilia

<https://www.nationwidechildrens.org/conditions/hemophilia>

[Hemophilia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hemophilia/diagnosis-treatment/drc-20373333)

[Hemophilia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK551607/)

### Von Willebrand Disease

**Definition and description**

Von Willebrand disease is the most common inherited bleeding disorder, caused by a deficiency or dysfunction of von Willebrand factor, a protein essential for blood clotting.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.

### What happens if you have von Willebrand disease?

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.

### causes of 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 factors. Factors are proteins that help your blood to clot.

You have the 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.

## Risk factors of von willebrand disease

The major risk factor is having a family history of von Willebrand disease. Parents pass on the defective gene to their offspring. Rarely can generations skip the sickness.

The disorder, which is an "autosomal dominant inherited" one, often requires a defective gene from just one parent to cause symptoms. If you carry the gene for von Willebrand disease, you have a 50% chance of passing it on to your children.

The most severe form of the condition is "autosomal recessive," which requires that both of your parents pass a defective gene on to you.

**Symptoms of von willebrand disease**

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.

**Diagnosis and Test**

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 level means 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.

**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.

## Prevention of von willebrand disease

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

## 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.

## 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.

# Differential diagnosis

Haemophilia A

## Factor VIII is reduced whereas von Willebrand factor ristocetin cofactor is normal, as is binding of factor VIII to von Willebrand factor.

## Pseudo (platelet type) von Willebrand disease

Pseudo von Willebrand disease is a **platelet disease** involving increased affinity of GPIb platelets for von Willebrand factor with variable levels of thrombocytopenia. Differential diagnosis between pseudo von Willebrand disease and type 2B von Willebrand disease can only be performed at specialised laboratories.

Acquired von Willebrand disease

Acquired VWF deficiency can be seen in certain clinical settings such as **lymphoproliferative and myeloproliferative syndromes, certain types of cancer and certain autoimmune diseases**, as well as in aortic valve stenosis.

This acquired deficiency may be related to the presence of auto-antibodies directed against VWF, to the adsorption of VWF at the surface of certain cells, or to degradation of VWF.

* Symptoms are generally moderate.
* Onset normally occurs after the age of 50 years.
* Laboratory signs are identical to those of von Willebrand disease.
* Disappearance of the disease following aetiological treatment may serve as a basis for retrospective diagnosis

**Epidemiology**

In a CDC study of 102 women with all types of VWD compared to 88 controls:

The most commonly reported bleeding symptoms among women with VWD were: heavy menstrual bleeding (95%), bleeding after minor injuries (92%), and excessive gum bleeding (76%)

* 74% of women with VWD reported excessive bleeding from several sites (e.g. nose, gum and uterus) or following several procedures or injuries (e.g. dental, surgical, childbirth and minor injury) compared to 6% of controls.
* 41% of women with VWD reported a diagnosis of migraine headaches compared with 13% of controls.
* 37% of women with VWD reported a diagnosis of arthritis compared with 15% of controls.
* 37% of women with VWD compared with 10% of controls indicated that their menstrual period limited routine work, social activities and had a negative effect on life.
* More women with VWD than controls in this study had undergone hysterectomy (25% vs. 9%).

In studies of 38 women3 and 42 men4 with Type 1 VWD (the most common form):

* The most common bleeding symptoms were heavy menstrual bleeding in women (93%) and nosebleeds in men (53%).
* 45% of women and 50% of men with VWD reported excessive bruising.
* 40% of women and 47% of men with VWD reported excessive bleeding with surgery.
* 34% of women and 29% of men with VWD reported dental bleeding.
* 21% of women and 26% of men with VWD had received a blood transfusion.
* 76% of men with VWD had been diagnosed by age 10, but 50% of women with VWD were not diagnosed until after age 12.

**Reference**

<https://www.cdc.gov/von-willebrand/data/index.html>

[von Willebrand Disease: What It Is, Types, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/17709-von-willebrand-disease)

### Thrombophilia (hypercoagulable Disorders)

**Definition and description**

Thrombophilia encompasses conditions that increase the risk of abnormal blood clots, such as deep vein thrombosis (DVT) or pulmonary embolism (PE), often due to genetic or acquired factors

Thrombophilia is a blood disorder that makes the blood in your veins and arteries more likely to clot. Healthcare providers call this a “hypercoagulable” condition because your blood coagulates or clots more easily. Thrombophilia can be an inherited (genetic) or acquired tendency to form blood clots in arteries and veins.

Normally, your body makes a blood clot when you cut your finger with a knife, for example. The blood clot stops the bleeding. Later, your body breaks the clot apart when it doesn’t need it anymore. When you have thrombophilia, your body makes too many blood clots or doesn’t break down the old ones.

Blood clots can cause clogs or blockages in your veins or arteries. This can hurt your major organs or cause a stroke or heart attack because your blood vessels carry the oxygen your cells need. A clog in your blood vessel keeps blood from getting to your cells.

#### Types of thrombophilia

There are two types of thrombophilia: the kind you’re born with (genetic) and the kind you get (acquired) in other ways.

* Acquired thrombophilia, which is more common than the inherited kind, comes from a variety of things, like medicines, your lifestyle or diseases. The most common acquired thrombophilia is antiphospholipid syndrome. It’s also the most aggressive thrombophilia.
* Genetic (inherited) thrombophilia is the type you get from one or both of your parents. The affected gene causes your body to make certain clot-forming proteins that don’t work the way they should. Some genetic issues make you unable to produce enough of a protein you need to stop clotting. You may have inherited thrombophilia if you’ve had miscarriages or blood clots before age 40. You may have a relative who had blood clots, too.

##### Types of genetic thrombophilia

Types of genetic thrombophilia include:

* Factor V Leiden thrombophilia: The most common type of genetic thrombophilia (affecting 1% to 5% of the population). People with this type have a higher risk of getting a first-event deep vein thrombosis (DVT), but probably not a higher risk for more blood clots after the first one.
* Prothrombin thrombophilia: The second most common type of genetic thrombophilia, affecting 1% to 5% of the general population. People with this type have a higher risk of first-event pulmonary embolism, deep vein thrombosis (DVT) or miscarriage, but probably not a higher risk for more blood clots after the first one.
* Protein C deficiency: Less common type, affecting less than 1% of people. This type of thrombophilia puts you at a higher risk of repeated blood clots. If you got it from both parents, it can be life-threatening.
* Protein S deficiency: Less common type, affecting less than 1% of people. An even rarer form (from both parents) can cause a life-threatening clotting issue in infants.
* Protein Z deficiency: This type can increase your risk of thromboembolisms and pregnancy complications (miscarriage and preeclampsia).
* Antithrombin deficiency: Less common type, affecting 1 in 500 to 5,000 people. But those who have it have a higher risk of blood clots than people with other inherited blood clotting disorders. More than 80% of people with this type of thrombophilia get at least one blood clot by age 50.

### symptoms of thrombophilia

You may not feel any thrombophilia symptoms unless you get a blood clot. Blood clot symptoms differ in various parts of your body:

Brain

* Seizures.
* Sudden headache.
* Difficulty talking or seeing.
* Feeling weak on one side of your body.

Heart

* Shortness of breath.
* Chest pain.
* Painful left arm.
* Sweating.
* Lightheadedness.
* Nausea.

Lungs

* Fast breathing.
* Fast heart rate.
* Shortness of breath.
* Painful deep breathing.
* Chest pain.

Belly

* Nausea.
* Throwing up.
* Pain in your belly.

Leg or arm

* Swelling.
* Pain.
* Warm feeling.

**causes** **of thrombophilia**

In addition to a genetic problem with a protein your body uses for clotting, causes of thrombophilia include other medical issues, like:

* Antiphospholipid syndrome.
* Disseminated intravascular coagulation (DIC), a rare blood clotting disorder.
* Hepatitis.
* HIV.
* Liver disease.

#### Risk factors of thrombophilia

Thrombophilia risk factors include:

* overweight.
* Being pregnant.
* Using tobacco products.
* Having atherosclerosis, cancer, diabetes, HIV or certain heart problems.
* Not moving your body for a long period of time.
* Having surgery or being in the hospital.
* Taking birth control pills containing estrogen.
* Taking hormone replacement therapy containing estrogen.
* Having a family history of blood clots.
* Being an older adult.
* Having unexplained miscarriages.
* Having more than one blood clot by age 40.

## Diagnosis and Tests

Your provider can make a thrombophilia diagnosis with:

* Your medical history.
* A physical exam.
* Blood tests to check for a genetic cause of thrombophilia.
* Tests that show what’s going on in your body.

You should get a test for thrombophilia if you get a blood clot and:

* You had a blood clot before age 50.
* You have a strong family history of blood clots.
* You have clots without a known cause (no risk factors).
* You have clots in unusual locations.
* You’ve had frequent miscarriages.
* Testing will influence the choice and length of time for blood thinner therapy.
* Your provider wants to test family members who may be at risk of developing blood clots.

Some conditions can give you a false positive test result, so make sure your provider knows your full medical history. Conditions that can affect test results include:

* Liver disease.
* A lack of certain vitamins.
* Nephrotic syndrome (a kidney issue).
* Pregnancy.

#### What tests will be done to diagnose thrombophilia?

Your provider may order thrombophilia testing that includes:

* Angiograms or venograms (X-rays that read a dye injection in your blood vessels).
* Ultrasound (using sound waves).
* Computed tomography (CT) scan (using X-rays and a computer).

## Management and Treatment

Although you can’t cure the kind of thrombophilia that you inherit, you can treat it.

Thrombophilia treatment for acquired or inherited types of the condition may include compression stockings for your legs or medicine to prevent or break up a blood clot. Some people may need surgery to remove a blood clot.

#### Specific medicines used

Providers order medications, such as:

* Blood thinners (anticoagulants) like heparin, warfarin (Coumadin® or Jantoven®) or newer blood thinners like rivaroxaban or apixaban.
* Thrombolytics (clot-dissolving drugs that providers use only in emergencies).

#### Side effects of blood thinners

Side effects of blood thinners may include:

* Bleeding too much when you get a cut.
* Having chills.
* Losing hair.
* Having nosebleeds.
* Having pain in your belly.

### How soon after treatment will I feel better?

It’s important to know that blood thinners don’t dissolve blood clots. They stabilize the blood clots so they don’t move or get bigger, and allow your body’s natural resources to absorb the clot over time.

But thrombolytics you get through an IV can dissolve clots quickly.

## Prevention of thrombophilia

You can’t prevent thrombophilia that you got from your parents, but you may be able to prevent some acquired thrombophilia.

If you’re at a high risk of blood clots, your provider may give you:

* Heparin after surgery if you’re at risk for a venous thromboembolism (VTE).
* Antithrombin injection before and after surgery if you don’t have enough antithrombin.
* Compression stockings or an intermittent pneumatic compression device if you’re at risk of a VTE.
* Alternatives to standard birth control pills, like certain intrauterine devices or pills that only have progestogen.
* A dose of heparin before a long flight.

You can lower your risk of acquired thrombophilia on your own by:

* Avoiding tobacco products.
* Staying at a weight that’s healthy for you.
* Walking around every hour or two on a long flight or car ride.
* Avoiding medicines that contain estrogen.
* Getting up and walking as soon after surgery as you can.
* Making exercise part of your routine.
* Getting treatment for medical conditions that can cause thrombophilia.
* Following your provider’s instructions for taking a blood thinner medication.
* Making sure you’re up to date with all cancer screenings your provider recommends for you. Cancer is a strong risk factor for developing blood clots.

## Outlook / Prognosis

Although your provider can’t cure genetic thrombophilia, they can order medicine like blood thinners for you to take for life. This medicine will help you manage your thrombophilia.

Nearly 90% of people who have thrombophilia never get a blood clot, but some people get one or more serious clots.

#### How long thrombophilia lasts

If you inherited thrombophilia, you’ll have it for life. Other kinds of thrombophilia can improve when you treat the condition that caused it.

## Living With

If you have thrombophilia, you may need to take medicine for life. You also need to be careful in situations where you could get a cut, like during meal preparation.

You may need to take blood thinners if your risk of forming more blood clots is high. With some of these medicines, you’ll need to have frequent checkups.

You may also want to find safer ways to cut food, brush your teeth or shave to prevent bleeding.

### When to see a doctor

Contact your provider if you think you’re having any of the signs and symptoms of a blood clot, including:

* Leg swelling you didn’t have before.
* Shortness of breath.
* Chest pain.

Contact your provider right away if you have issues with the blood thinner you’re taking, like nosebleeds or blood in your urine (pee) or poop.

### complications of thrombophilia

Blood clots can travel all over your body, limiting or blocking blood flow to your organs. This can cause serious problems in your:

* Lungs (pulmonary embolism).
* Heart (heart attack).
* Brain (stroke).
* Kidneys (kidney failure).
* Leg or arm veins (deep vein thrombosis or DVT).
* Leg and pelvis arteries (peripheral artery disease or PAD).
* Developing fetus (miscarriage)

## Differential Diagnosis

## For investigation of patients suffering from thrombotic events, it is essential to differentiate provoked and unprovoked thrombosis through history and physical. Thrombotic events are observable under diverse conditions. Therefore a broad differential diagnosis is essential including the more frequent (immobilization, travel) and less frequent entities such as cardiac disease (atrial fibrillation, cardiomyopathy, mitral valve prolapse, prosthetic valves), non-bacterial thrombotic endocarditis (NBTE) and hematologic causes such as disseminated intravascular coagulopathy (DIC) and heparin-induced thrombocytopenia (HIT). Clinical decision aids such as the HIT score can help to evaluate pretest probability and guide diagnostic workup.

## Thrombophilia should be a differential diagnosis for vaso-occlusive events. Arterial thrombosis such as osteonecrosis, ischemic stroke and myocardial infarction can be related to thrombophilia. Celik et al. investigated a population of young patients suffering from myocardial infarction. They concluded that the established cardiovascular risk factors but not thrombophilias contributed to myocardial infarction in young patients. Other studies suggest thrombophilia in the differential diagnosis of myocardial infarction with non-occlusive coronary arteries (MINOCA). Thrombophilias might also be associated with stroke in young people by venous thromboembolism through a patent foramen ovale.

## Thrombophilias must be differentiated from other diseases that cause the following clinical presentations:

## Family history of thrombosis, especially at an early age (< 45 years

## Unprovoked thrombosis at an early age (<40-55 for [venous thrombosis](https://www.wikidoc.org/index.php/Venous_thrombosis) and <50-55 for [arterial thrombosis](https://www.wikidoc.org/index.php/Arterial_thrombosis))

## Recurrent [thrombosis](https://www.wikidoc.org/index.php/Thrombosis) including deep venous thrombosis, pulmonary embolism, or superficial venous thrombosis

## Thrombosis at multiple sites, or unusual locations including in cerebral, hepatic, portal, mesenteric, and renal veins

## Thrombosis in [arteries](https://www.wikidoc.org/index.php/Arteries) with the absence of arterial disease

## History of fetal loss

## History of warfarin skin necrosis

### EPIDEMIOLOGY

### Incidence

* The epidemiology of thrombosis varies depending upon the following factors:
  + Venous vs Arterial
  + Provoked vs Unprovoked
  + First episode vs Subsequent episode
* **Inherited thrombophilia:** The incidence of incident and recurrent venous thrombosis in inherited disorders is approximately 150-840 and 3,500-10,500 per 100,000 individuals respectively.
* **Venous thromboembolism:** It is the second most common cardiovascular disorder following myocardial infarction and more frequent than stroke with the incidence range of 1-5 in 1000 per year in the general population. Its annual incidence is age dependent which follow as:
  + **Children:** 1 per 100000 per year
  + **Adults:** 1 per 1000 per year
  + **Elderly:** 1 per 100 per year
* **Frequency of thrombophilias:**
  + **APS, APC resistance, elevated factor VIII:** 25 to 28%
  + **Protein C deficiency, Protein S deficiency, Hyperhomocysteinemia and Prothrombin mutation:** 5 to 10%
  + **Pulmonary embolism:** 29 to 48 per 100000 person-years
  + **Deep vein thrombosis:** 45 to 117 per 100000 person-years

### Prevalence

The prevalence of thrombophilia in Caucasian populations is:

| **Inherited thrombophilia** | **Healthy subjects/General population (%)** | **Patients with recurrent thrombosis (%)** |
| --- | --- | --- |
| Factor V Leiden | 1 - 20 | 18 - 50 |
| Prothrombin G20210A | 2 - 8 | 7 - 20 |
| Antithrombin deficiency | 0.02-2 | 1 - 5 |
| Dysfibrinogenemia | <1 | <1 |
| Protein C deficiency | 0.2 - 5 | 3 - 10 |
| Protein S deficiency | 0.3 - 3 | 2 - 10 |
| Hyperhomocystenemia | <5 | <10 |
| Elevated factor VIII levels | 11 | 25 |

### Age

* Thrombophilias may develop in patients irrespective of their age groups.
* **Acquired thrombophilias**: They are more commonly observed among **elderly** patients who are more than 60 years old.
* **Inherited thrombophilias:** **Young** patients between 40-55 years old more likely carry the risk of inherited thrombophilias.

### Gender

* Several epidemiologic studies have reported mixed results regarding the effect of gender on venous thrombosis.
* Certain groups observed an increased risk of thrombosis in **younger females and older males**, while others found similar frequencies in both the genders.
* Christiansen et al conducted a prospective follow up study in patients with inherited thrombophilias, and revealed an age corrected hazard ratio of 2.7 for recurrent thrombosis in male patients compared to women. [[14]](https://www.wikidoc.org/index.php/Thrombophilia_epidemiology_and_demographics#cite_note-pmid15900005-14)

### Race

* The Factor V Leiden G1691A and prothrombin G20210A mutations usually affect individuals of the **Caucasian race** in comparison to non-white individuals.
* Factor V Leiden
* The most frequent form of inherited thrombophilia is Factor V Leiden with **20-50% prevalence** in patients with r**ecurrent venous thrombosis**.
* The prevalence of Factor V Leiden thrombophilia in African and Asian populations is approximately **500 per 100,000 individuals** worldwide.

#### Prothrombin G20210A

* The **second most** frequent form of inherited thrombophilia is prothrombin G20210A.
* Its prevalence in African and Asian populations is approximately **600 per 100,000 individuals** worldwide.

#### Protein C deficiency

* **Mild protein C deficiency:** 1 in 200 to 1 in 500 individuals.
* **Clinically significant protein C deficiency:** 1 in 20000 people.
* **Severe protein C deficiency:** Rarely found among 1 in 4 million infants which may be attributable to underdiagnosis or under-reporting.

REFERENCE

[Thrombophilia epidemiology and demographics - wikidoc](https://www.wikidoc.org/index.php/Thrombophilia_epidemiology_and_demographics#:~:text=The%20prevalence%20of%20thrombophilia%20in%20Caucasians%20is%20approximately,approximately%20150-840%20per%20100%2C000%20person%20years.%20%5B6%5D%20)

### 

### 

### 

### Hemoglobinopathy

**Definition and description**

Hemoglobinopathy is a group of inherited blood disorders that affects your hemoglobin. Hemoglobin is a protein in your red blood cells. It helps carry oxygen throughout your body.

Hemoglobinopathy runs in families. It happens because of a genetic variation (gene change) that your biological parents can pass down to you. It’s the most common type of inherited blood disorder, affecting millions of people worldwide. By definition, the term “hemoglobinopathy” includes all inherited hemoglobin disorders. Researchers have identified over 600 types.When your body makes abnormal hemoglobin — or doesn’t make enough of it — it can cause symptoms like pain, fatigue and organ damage. Early detection is key. That’s one reason healthcare providers screen newborns for hemoglobinopathies immediately after birth.

## Hemoglobinopathy isn’t curable. But you can manage symptoms and avoid complications with treatment.

#### Types of hemoglobinopathy

## There are hundreds of types of hemoglobinopathies. Many of their names contain letters. These letters represent different variants of the hemoglobin protein (and the order in which researchers discovered them). This gives healthcare providers information about the specific genetic variation responsible for the abnormality.

## Some of the most common hemoglobinopathies are:

## Hemoglobin C disease: Hemoglobin C replaces normal hemoglobin

## Hemoglobin E disease: Hemoglobin E replaces normal hemoglobin

## Hemoglobin D disease: Hemoglobin D replaces normal hemoglobin

## Hemoglobin SC disease: You inherit one sickle cell gene and one hemoglobin C gene

## Hemoglobin SD disease: You inherit one sickle cell gene and one hemoglobin D gene

## Hemoglobin SE disease: You inherit one sickle cell gene and one hemoglobin E gene

## Sickle cell disease: Your red blood cells are sickle-shaped

## Thalassemias: Your body doesn’t make enough hemoglobin

## Symptoms of hemoglobinopathy

## Symptoms of hemoglobinopathy include:

## Cold hands and feet

## Dark pee

## Fatigue

## Growth delays (in children)

## Jaundice

## Pale skin

## Shortness of breath

## Sleeping longer than usual

## Swelling in your hands and feet

## Babies with severe hemoglobinopathies often have symptoms soon after they’re born. Other times, symptoms don’t appear until childhood. Adults with hemoglobinopathy may experience these symptoms during a flare-up (like a sickle cell crisis).

## causes of hemoglobinopathy

## Hemoglobinopathy happens when you have a gene variation affecting your hemoglobin. You get the gene change from one or both of your biological parents.

#### Risk factors

## You’re more likely to have hemoglobinopathy if you:

## Are of African, Mediterranean, Southeast Asian or West Asian descent

## Have a biological parent or sibling with hemoglobinopathy

## Live in an area where newborn hemoglobinopathy screenings aren’t routine

## If you have hemoglobinopathy, you’re more likely to have a child with the disorder.

### Complications of hemoglobinopathy

## Anemia. Some forms of hemoglobinopathy can lower your red blood cell count and cause anemia.

## Frequent infections. Hemoglobinopathy can cause a compromised immune system, which can increase your risk for infection.

## Organ damage. Hemoglobinopathy reduces oxygen levels in your blood. Over time, a lack of oxygen-rich blood can lead to tissue and organ damage.

## Pain episodes. Some types of hemoglobinopathies, like sickle cell disease, can cause blockages in your blood vessels. This restricts blood flow and results in pain.

## Diagnosis and Tests

## Healthcare providers use several different tests to diagnose hemoglobinopathy, including:

## Complete blood count (CBC). This is typically the first blood test your provider will do. It tells them information about your blood cells, like how many of each type you have.

## Genetic testing. Your healthcare provider can do this test to identify specific gene variations.

## Hemoglobin electrophoresis. This test separates hemoglobin molecules from your blood sample to see if they’re abnormal.

## Iron studies. Your provider might do this test to find out if you have iron-deficiency anemia.

## Newborn screening. Many areas routinely test newborn babies for hemoglobinopathy, including Canada and most of the U.S.

## Prenatal testing. You can have this test done during pregnancy to see if the fetus has hemoglobinopathy.

## Management and Treatment

## Blood transfusions. Some hemoglobinopathies, like thalassemia and sickle cell disease, affect the amount of hemoglobin in your blood. You may need a blood transfusion so you have normal hemoglobin levels.

## Folic acid. These supplements may be able to boost red blood cell production.

## Gene therapy. Scientists take affected cells from your body, use special tools to fix them and then, put them back into your body. It’s like rewriting the instructions in your genes.

## Iron chelation therapy. If you have extra iron in your body, iron chelation therapy can remove it. You take this medication by mouth or injection.

## Oxygen therapy. Your healthcare provider may recommend oxygen therapy in combination with other treatments. The goal is to boost oxygen in your blood and reduce pain episodes.

## Stem cell transplant. This replaces abnormal red blood cells with healthy ones. This isn’t common because it can be difficult to find suitable donors. It also raises your risk of graft vs. host disease (GvHD).

## Treatments vary depending on your unique situation. You may not need treatment if you have a very mild form of hemoglobinopathy. Be sure to ask your healthcare provider what’s best based on the type of hemoglobinopathy you have.

### How soon after treatment will I feel better?

## It depends on the type and severity of hemoglobinopathy you have. Most people feel better in a few weeks or months after starting treatment.

## Hemoglobinopathy is a lifelong condition. You’ll need regular check-ups and monitoring. Your healthcare provider can help you find ways to ease your symptoms.

## Outlook / Prognosis

## Your outlook is good with the right treatment. Over 90% of people with hemoglobinopathy survive into adulthood.

## Without treatment, many hemoglobinopathies result in death during the first few years of life. Early diagnosis is key and can help you avoid serious complications.

## Prevention

## No, you can’t prevent hemoglobinopathy because you inherit it. But you can manage your symptoms with appropriate treatment.

## Living With

### How do I take care of myself?

## Living with hemoglobinopathy can be challenging. Taking care of yourself can reduce your risk for pain and other side effects.

## Here are some general guidelines:

## Drink lots of water.

## Be physically active, but don’t overdo it.

## Eat foods that are rich in iron, vitamins and minerals.

## Manage your stress with meditation, yoga or other forms of mindfulness.

## Wash your hands frequently to help reduce your risk of infection.

### When to see a doctor

## You should tell a healthcare provider if you experience fatigue, shortness of breath, pale skin or other symptoms.

## If you’ve already been diagnosed with hemoglobinopathy, call your provider if your symptoms come back or get worse. They may need to adjust your treatment.

**EPIDEMIOLOGY**

Identification of healthy carriers can be achieved through simple haematological tests and this makes screening on a population scale possible. The same tests may be used for epidemiological surveys designed to estimate the proportion of carriers in a given population. The carrier rate can be measured from both surveys and screening programmes and it will give an overall indication on the size of the problem in a given population and identify at-risk groups within a population.

In a prevention programme the number of individuals to be screened will depend on whether it is necessary for the whole population of reproductive age to be identified, as is the case in high prevalence areas, or whether targeted screening of at-risk groups is required, as is the case where the genes are present in ethnic minorities. The service indicator for screening varies therefore according to the policy which suits the population structure.

The haematological characteristics of thalassaemia carrier states should be established for each population since in many populations there is interaction of various genes, which may alter the usual haematological manifestations of the heterozygote. This is necessary in order to avoid errors in carrier identification.

In many populations surveys have already been carried out. In these surveys, samples of 1000 or less have been used in most cases. The smaller the sample the more likely it is that a selection error has been introduced. A ‘biased’, selected sample will not represent the whole population. Such bias often occurs because target groups are chosen for convenience and accessibility and may not reflect the characteristics of all the people. For example, if university students are chosen because the investigating team has easy access to this group, care must be taken that they do not come from a racial or social minority.

The target population should therefore be defined according to how much it reflects the total population or whether it represents a particular sub-group. It is acceptable to use inclusion criteria based on accessibility e.g. 17-18 year old school leavers, provided schools from all areas are included. Army recruits or blood donors may be used if they are drawn from all sections of society. In a small country with a small homogeneous population (e.g. Cyprus or Malta) a random sample of 1000 is acceptable. In large, compound populations, it will be necessary to divide the population into well-defined subgroups (stratification). A sample from each group separately should be taken, ensuring random sampling from within each group. The final total sample must include the right proportion of each subgroup. In this way information will be obtained both about the total population and how the subgroups differ from each other. Knowledge of the distribution, both geographically and in specific groupings of the population (micromapping), is important for the accuracy but also for practical application of the epidemiological information such as directing services, both preventive and curative. In this respect knowledge of population size and characteristics derived from basic demographic data, including size, composition (ethnic groups, migrants), birth rates, and whether consanguineous marriage is common are all important data to be recorded. Migration has introduced haemoglobinopathy genes to areas of low prevalence, especially in Europe and the Americas.

The host countries are often unprepared for these new health problems while the migrants themselves, especially in the first generation, are often of a low socioeconomic and educational level and make poor use of local services. The language and cultural differences are barriers to effective educational and counselling activities in such sensitive areas as genetic prevention

. Customary consanguineous marriage may be common in many migrant populations as it is in the countries of origin. This practice will tend to increase the affected births of rare recessively inherited disorders and must be considered when assessing the expected births. Where this is the case there will be a clustering of cases within extended family groups, making family screening a productive exercise. It also means that patients with thalassaemia have a greater chance of having an HLA compatible sibling donor for stem cell transplantation, which is a consideration in planning services for patient care.

This kaleidoscope of epidemiological situations emphasises the need for a clear understanding of the individual country situation.

REFERENCES

[EPIDEMIOLOGY OF HAEMOGLOBINOPATHIES - Prevention of Thalassaemias and Other Haemoglobin Disorders - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK190485/)

## [Hemoglobinopathy: What It Is, Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/hemoglobinopathy#overview)

### 

### 

### Hemolytic anemia

**Definition and description**

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.

### Who is affected by hemolytic anemia?

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

### What’s the difference between 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 medication

**Causes of hemolytic anemia**

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 rickettsii* 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.

### symptoms of hemolytic anemia

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.

### What tests do healthcare providers use to diagnose hemolytic anemia?

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.

**DIFFERENTIAL DIAGNOSIS**

One of the main laboratory values that aids in the diagnosis of hemolytic anemia is an elevated reticulocyte count, as the bone marrow is attempting to produce increased amounts of RBCs. This can be seen in other disease processes such as blood loss anemia; therefore, one must be cautious in taking a thorough history as well as evaluating other lab values that should also be altered, including LDH, haptoglobin, and indirect bilirubin.

Hemolysis can be seen in many rare conditions from paroxysmal nocturnal hemoglobinuria to blood transfusions or mechanical circulatory support; therefore, a wide differential must be ruled out.However, to assist one in making this distinction, there have been case reports that help separate intravascular hemolysis from diseases such as PNH, from those like heart valves with mechanical prosthesis as kidney injury is less seen in the latter unless there is underlying kidney disease

**EPIDEMIOLOGY**

Through these databases, one can see there is no difference in hemoglobin values of men from 20 to 59 or women 20 to 49. This assists in studying patient populations whose values do fall out of the norm from these ranges.

African Americans are found to have a lower limit of normal hemoglobin concentration, lower serum transferrin saturation, higher serum ferritin levels, lower bilirubin levels, and lower leukocyte counts. This is thought to be due to the higher frequency of alpha-thalassemia and G6PD deficiency in the black population. G6PD deficiency is known to affect millions of people worldwide.

Although it can be seen worldwide, HE is most predominantly seen in malaria-endemic regions of West Africa. Several forms of anemia are seen in these regions, as it is often thought to be protective against malaria.

Overall hemolytic anemias cover a broad range of age groups, races, and both genders as several subcategories can be acquired or inherited.

REFERENCES

[Hemolytic Anemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK558904/#article-22737.s10)

[Hemolytic Anemia: Symptoms, Treatment & Causes](https://my.clevelandclinic.org/health/diseases/22479-hemolytic-anemia)

### 

### 

### Fanconi anemia (FA)

**Definition and description**

Fanconi anemia (FA) is a rare inherited condition that affects your bone marrow and many other parts of your body. Your bone marrow is the spongy tissue in the center of your bones that creates stem cells that become red and white blood cells and platelets. If you have Fanconi anemia, your bone marrow doesn’t create healthy blood cells and platelets. People with FA have an increased risk of developing blood disorders and some kinds of cancer. FA also causes physical abnormalities that can affect people’s organs and appearances. People with FA that’s caused blood disorders are living longer and with fewer medical issues because they’re able to have bone marrow transplants.

### How does Fanconi anemia affect my or my child’s body?

Fanconi anemia may affect your or your child’s body in many different ways:

* About 75% of children born with FA have physical abnormalities that may affect their appearance and some of their internal organs.
* About 90% of people with FA have bone marrow failure or lack of function. That means their bone marrow doesn’t make enough healthy blood cells. People with bone marrow failure can develop blood disorders such as aplastic anemia and myelodysplastic syndrome (MDS). MDS is a form of pre-leukemia.
* Between 10% and 30% of people with FA develop certain cancers, including leukemia. They may have cancer at earlier ages than people who don’t have Fanconi anemia.

### Is Fanconi anemia a cancer?

FA isn’t cancer, per se. People who have FA are more likely to develop certain cancers, including acute myeloid leukemia, skin cancer, cancer of the head and neck and other parts of their bodies.

## Symptoms of fanconi anemia

Fanconi anemia affects people in many different ways, starting with how our bodies develop during gestation. FA may cause different symptoms linked to many different conditions, including anemia, bone marrow failure syndrome (aplastic anemia), cancer and physical abnormalities. For example, someone with FA may be very short or have problems with their bone structure. Many people have FA but don’t have obvious signs or symptoms.

### What are anemia symptoms?

Anemia is a common sign of FA. Symptoms include:

* Fatigue. People with anemia may feel too tired to carry on with their daily activities.
* Pale skin color.
* Difficulty catching their breath.
* Feeling as if their heart is racing.
* Headaches.

### What are bone marrow failure syndrome symptoms?

Bone marrow failure syndrome (aplastic anemia) symptoms are similar to anemia symptoms. Other symptoms are:

* Bacterial or fungal infections: FA can cause low white blood cell count that increases the risk of infections.
* Excessive bleeding:FA affects platelets, which helps blood to clot and control bleeding. People may bleed from any part of their body including their gums, nose and gastrointestinal tract.

### What are common symptoms of cancer associated with FA?

People with FA are more likely to develop some kind of cancer. Symptoms for some common cancer types include:

* Myelodysplastic syndrome and acute myeloid leukemia (AML): Symptoms include fatigue, easy bruising or bleeding, pale skin and anemia, shortness of breath and severe infection.
* Squamous cell carcinoma: Rough-feeling bumps or growths and sores that don’t heal.

### What are common symptoms of physical abnormalities associated with FA?

FA can affect people’s appearance and how their bodies work. For example, some people with FA are smaller and shorter than normal. Sometimes, FA affects the size and shape of people's ears, feet, arms and hands. Other times, it affects the shape and function of their internal organs, such as their hearts, livers and kidneys. Some symptoms include:

* Having oddly shaped thumbs, two thumbs on one hand or no thumbs.
* Having a noticeably smaller head. This is a symptom of microcephaly. Babies born with microcephaly may have problems learning how to speak, stand and walk.
* Having an unusually large head. This is a symptom of hydrocephalus. Babies born with hydrocephaly may develop balance problems, vision problems and problems learning how to speak, stand and walk.
* Hearing loss or hearing difficulties. Sometimes, FA causes unusually small ears that affect peoples’ ability to hear.
* Skin that has large light-brown colored patches. Light-brown spots on skin, sometimes called café-au-lait spots.
* Unusual spinal curves. This is a symptom of scoliosis.

### Causes of Fanconi anemia

FA is a genetic disorder caused by inherited mutations (discrete changes in genetic code) in a group of genes (genetic blueprints) for proteins. We have about 20 FA genes, but not all of them are affected when genes mutate. FA genes protect us from DNA damage that happens throughout life. When FA genes mutate, proteins that typically repair routine DNA damage don’t work properly and can’t fix damaged DNA. Here’s what happens:

* The DNA damage continues to spread, causing abnormal cell growth or cell death.
* Abnormal cell death can cause physical abnormalities linked to FA, as well as reduce the amount of blood cells our bodies need to function.
* Abnormal cell growth can lead to acute myeloid leukemia or other types of cancer.

### Can someone who has abnormal FA genes pass them on to their children?

There’s a 25% chance that parents who carry abnormal FA genes will have a child who develops symptoms. And there’s a 25% chance that parents who carry abnormal FA genes won’t pass those abnormal genes on to their child.

## Diagnosis and Tests

Most of the time, healthcare providers diagnose Fanconi anemia while investigating or treating related conditions, including cancer, progressive bone marrow failure or physical abnormalities.

* Physical abnormalities: About 60% of people diagnosed with FA have physical abnormalities that affect the shape and size of parts of their bodies and organs.
* Progressive bone marrow failure: About half of children and adults who have FA have symptoms of bone marrow failure. Most children with FA develop bone marrow failure symptoms by age 10. Nearly all adults who have FA develop these symptoms by age 50.
* Cancer: People who have FA often develop acute myeloid leukemia (AML) or tumors in their head, neck, skin, gastrointestinal system or genital tract. About 30% of adults who have FA were receiving cancer treatment when diagnosed with FA.

As a result, healthcare providers typically diagnose the conditions that FA causes and then diagnose FA. Tests healthcare providers may use to diagnose blood disorders, blood cancers and solid tumors include:

* Complete blood count (CBC):Healthcare providers use this test to evaluate blood cell health and activity.
* 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.
* Basic metabolic panel (BMP): This test provides information about your body’s chemical balance and metabolism (how your body transforms the food you eat into energy).
* Bone marrow biopsy: Healthcare providers examine bone marrow cells to diagnose certain diseases.
* Magnetic resonance imaging (MRI): This test produces detailed images of your organs.
* Ultrasound: This is an imaging test that uses sound waves to evaluate symptoms and health conditions.

Once your healthcare provider diagnoses the condition, they then determine if FA caused it.

Some genetic tests healthcare providers may use include:

* Chromosome breakage test,uses certain chemicals to see how chromosomes in blood and skin cells react.
* Genetic screening looks at specific genes to see if they have abnormalities that cause FA.

### I’m pregnant and have a family history of FA. What tests show if the fetus has FA?

Healthcare providers may test for FA using two common prenatal tests:

* Amniocentesis: Healthcare providers examine chromosomes from a fluid sample of your amniotic sac (the fluid-filled sac around the fetus).
* Chorionic villus sampling: Healthcare providers take a tissue sample from your placenta to look for signs of genetic changes related to FA.

## Management and Treatment

Typically, healthcare providers focus on treatments to manage blood disorders that FA causes, including:

* Bone marrow transplant: Healthcare providers may recommend a bone marrow transplant to treat leukemia, pre-leukemia or bone marrow failure.
* Androgen therapy: This treatment stimulates your red blood cell production. Healthcare providers may recommend this treatment if you have anemia.
* Synthetic growth factors: Growth factors stimulate your bone marrow to make more red and white blood cells. Healthcare providers may recommend synthetic versions to boost bone marrow blood cell production.
* Surgery: Healthcare providers may use surgery to correct physical abnormalities or repair damaged organs.

## Outlook / Prognosis

FA affects people in different ways. If you have FA, your healthcare provider is your best resource for information about your prognosis.

## Prevention

Fanconi anemia is an inherited disorder. That means you can’t reduce your risk of developing FA. That said, if you have a family history of FA, you may want genetic testing to find out if you’re carrying FA. Not everyone who carries FA develops medical conditions. Likewise, not all people who carry FA pass it on to their children. Genetic testing will help you to understand your situation.

## Living With

If you have Fanconi anemia, you’ll need to monitor your overall health and let your healthcare provider know if you notice changes in your body that may be signs of FA symptoms. Here are some examples:

* FA happens when something turns some normal genes into abnormal genes. Healthcare providers call this intrinsic genetic instability. Genetic instability may increase the chance that cancer-causing substances like tobacco will cause more harm than usual.
* FA increases your risk of developing cancer, especially skin cancer. While everyone should protect their skin and monitor for signs of skin cancer, people who have FA need to be especially vigilant.
* FA causes blood disorders. If you have FA, you should protect yourself from injuries that may cause bleeding. You should also watch for changes in your body, like bruising and unusual bleeding or feeling unusually tired. These may be signs of blood disorders like anemia or leukemia.

### I had a successful bone marrow transplant that treated my blood disorders. Do I still need to monitor my health?

Yes. Fanconi anemia can affect all parts of your body. While blood marrow transplants have cured FA blood disorders, people with FA are still more likely to develop cancer. Talk to your healthcare provider about steps you can take to protect your health.

**EPIDEMIOLOGY**

Fanconi anemia has been reported in persons of all races. However, owing to founder effects, the heterozygote frequency is greater in South African Afrikaners,sub-Saharan Blacks, and Spanish Romathan in the overall world population, leading to expected birth rates in these subpopulations of around one case per 40,000 births. Among Ashkenazi Jews in the United States, the carrier frequency is approximately 1 case per 90 people, with a projected birth rate of one case per 30,000 people.

The male-to-female ratio in the literature cases is 1.2:1, although equal numbers are expected in a disorder with over 99% autosomal recessive inheritance.

Fanconi anemia has been diagnosed in patients from birth to middle age, with a median age of 7 years. Individuals with birth defects are diagnosed at younger ages than are persons without birth defects.

**DIFFERENTIAL DIAGNOSIS**

Aplastic Anemia

* + Acquired bone marrow failure without congenital anomalies.
  + Usually lacks the chromosomal breakage seen in FA.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

* + Characterized by hemolytic anemia and thrombosis, but no congenital malformations or chromosomal instability.

Other Chromosomal Breakage Syndromes

* + Bloom Syndrome
  + Nijmegen Breakage Syndrome
  + Werner Syndrome
  + These syndromes also have DNA repair defects but differ in clinical presentation and genetic causes.

Inherited Bone Marrow Failure Syndromes (IBMFS)

* + Dyskeratosis Congenita (telomere biology disorder)
  + Shwachman-Diamond Syndrome
  + Diamond-Blackfan Anemia
  + These share bone marrow failure and cancer predisposition but have distinct genetic and clinical features.

Congenital Malformation Syndromes with Overlapping Features

* + Holt-Oram Syndrome (limb defects, heart anomalies)
  + Baller-Gerold Syndrome (craniosynostosis, radial aplasia)
  + Thrombocytopenia-Absent Radius (TAR) Syndrome
  + VACTERL Association (vertebral, anal, cardiac, tracheoesophageal, renal, limb anomalies)
  + Dubowitz Syndrome
  + Seckel Syndrome
  + These syndromes may have limb abnormalities and growth retardation but differ in hematologic involvement.

Other Causes of Pancytopenia or Macrocytosis

* + Nutritional deficiencies (e.g., B12 or folate deficiency)
  + Congenital infections
  + Exposure to teratogens

REFERENCE

[Fanconi Anemia: Background, Etiology, Epidemiology](https://emedicine.medscape.com/article/960401-overview#a5?form=fpf)

[Fanconi Anemia: What It Is, Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/14473-fanconi-anemia-fa)

**CRYOGLOBULINEMIA**

**Definition and description**

Cryoglobulinemia is a family of rare conditions, called vasculitis. Vasculitis causes irritation and swelling, called inflammation, of the blood vessels.

Cryoglobulins are atypical proteins in the blood. For people who have cryoglobulinemia (kry-o-glob-u-lih-NEE-me-uh), these proteins may clump together at body temperatures below 98.6 F (37 C).

These clumps can block blood flow. This can damage the skin, joints, nerves and organs, mainly the kidneys and liver.

Types

There are three types of cryoglobulinemia.

* **Type 1.** This type has one kind of atypical protein, called monoclonal. Type 1 most often is linked to blood cancers.
* **Type 2.** This has two types of atypical protein, both monoclonal and polyclonal. Type II most often is linked to hepatitis C virus.
* **Type 3.** This has a mix of polyclonal proteins. Type 3 most often is linked to autoimmune diseases such as rheumatoid arthritis.

**CAUSES of cryoglobulinemia**

It's not clear what causes cryoglobulinemia. It's been linked to:

* **Infections.** Hepatitis C is the most common infection linked to cryoglobulinemia. Others include hepatitis B, HIV, Epstein-Barr, toxoplasmosis and malaria.
* **Certain cancers.** Some cancers of the blood, such as multiple myeloma, Waldenstrom macroglobulinemia and chronic lymphocytic leukemia, can cause cryoglobulinemia.
* **Autoimmune diseases.** Disease in which the immune system attacks healthy tissues by mistake, called autoimmune, increases the risk of getting cryoglobulinemia. Examples are lupus, rheumatoid arthritis and Sjogren syndrome.

**RISK FACTOR**

Risk factors of cryoglobulinemia may include:

* **Sex.** Cryoglobulinemia happens more often in women than in men.
* **Age.** Symptoms of cryoglobulinemia most often begin in middle age.
* **Other diseases.** Cryoglobulinemia is linked with diseases such as hepatitis C, HIV, multiple myeloma, Waldenstrom macroglobulinemia, lupus and Sjogren syndrome.

**SYMPTOMS**

Some people have no symptoms of cryoglobulinemia. For people who have symptoms, the symptoms might come and go. They can include:

* **Skin spots.** Most people with cryoglobulinemia get purple skin spots, called lesions, on their legs. On Black or brown skin, the spots might look black or brown. Some people also get open leg sores, called ulcers.
* **Joint pain.** Symptoms like those of rheumatoid arthritis are common in cryoglobulinemia.
* **Peripheral neuropathy.** Cryoglobulinemia can damage the nerves at the tips of the fingers and toes. This causes numbness and other problems.

**DIAGNOSIS AND TEST**

Diagnosis of cryoglobulinemia involves a blood test. The blood is kept at body temperature, 98.6 F (37 C), for a time. Then it's cooled before being tested. The sample must be handled this way to get correct results.

Other blood and urine tests also might be used to find the underlying cause.

**TREATMENT**

Treatment depends on the cause of cryoglobulinemia and how bad it is. Watchful waiting might be a choice if you have no symptoms. Treatment may include medicines that calm the immune system or fight viral infections. For severe symptoms, a treatment that swaps blood plasma for donor plasma or another fluid might be used.

Even with treatment, cryoglobulinemia often returns. You might need regular follow-up visits with your health care professional to watch for its return.

**Lifestyle and home remedies**

If you have cryoglobulinemia, it's important to stay out of cold temperatures. Protect your fingers and toes. You may want to wear gloves when using the freezer or refrigerator. Check your feet daily for sores. Cryoglobulinemia can make it harder for foot damage to heal.

**COMPLICATION**

Cryoglobulinemia can affect the kidneys. The main symptoms are protein or blood in the urine. High blood pressure most often goes with the kidney symptoms. In time, kidney failure might happen.

**DIFFERENTIAL DIAGNOSIS**

Cryoglobulinemia must be diagnosed carefully, as its clinical presentation is similar to other vasculitides affecting small- or medium-sized vessels. The differential diagnosis of cryoglobulinemia include:

* Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (such as granulomatosis with polyangiitis [Wegener], eosinophilic granulomatosis with polyangiitis [Churg-Strauss], and microscopic polyangiitis).
* IgA vasculitis (Henoch-Schönlein purpura); Henoch Schlein purpura (HSP) causes palpable purpura in lower extremities but can be differentiated by immunofluorescence of skin biopsy. In HSP, immunofluorescence usually shows the deposition of IgA and not immune complexes.
* Cutaneous small-vessel vasculitis.
* Hypersensitivity vasculitis.
* Vasculitis is associated with a connective tissue disorder (such as SLE, rheumatoid arthritis, and Sjögren syndrome). Systemic lupus erythematosus can cause cutaneous vasculitis, cytopenias, arthralgias, positive RF, and glomerulonephritis. Further, there can be overlap with patients with underlying systemic lupus erythematosus developing cryoglobulinemic vasculitis. Systemic lupus erythematosus is usually associated with low complements, both C3 and C4, and not just isolated C4 depletion. Serum cryoglobulin detection and pathological evaluation are critical in differentiating these two conditions.  
  Rheumatoid arthritis is associated with joint pain and a positive RF. Rarely, leukocytoclastic vasculitis can be seen in rheumatoid arthritis as well. However, rheumatoid arthritis is associated with the presence of inflammatory arthritis and synovitis, which is usually absent in cryoglobulinemic vasculitis, where patients have arthralgias but usually lacks true synovitis. Further, anti-CCP antibodies are specific for rheumatoid arthritis and are not seen in cryoglobulinemic vasculitis. Renal involvement is rare in rheumatoid arthritis. Complements are usually normal in rheumatoid arthritis. Cryoglobulins will be absent.  
  Systemic sclerosis can cause cutaneous manifestations like digital ulcers and gangrene. However, other clinical features of systemic sclerosis, including sclerodactyly, calcinosis, interstitial lung disease, gastrointestinal dysmotility, are not seen in cryoglobulinemic vasculitis. Renal involvement in systemic sclerosis is rare and is manifested as scleroderma renal crisis which is different from cryoglobulinemic vasculitis induced glomerulonephritis. Both of these can be differentiated by kidney biopsy.

Other thrombotic and embolic disorders, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, should also be considered in the differential diagnosis. Additionally, patients affected by chronic HCV infection may develop arthralgias and membranoproliferative nephritis even without cryoglobulinemia. Therefore, further testing is necessary to reach a definitive diagnosis.

**PROGNOSIS**

When assessing the prognosis of cryoglobulinemia, the patient's underlying condition must be considered to determine the disease's extent accurately. Specifically, when considering type 1 cryoglobulinemia, hematologic diseases are often a preexisting condition. Studies have shown that the presence of cryoglobulins in the blood does not indicate a higher mortality rate.

Survival rates with cryoglobulinemia are 70% after 10 years of evident symptoms and approximately 50% 10 years after diagnosis. The prognosis largely depends on comorbidities and their severity, as well as the effectiveness of treatment. Recent trials with the CD-20 antibody rituximab have shown some beneficial results, and its use is being favored.

HCV-related cryoglobulinemia vasculitis is a significant disease with an approximate 5-year mortality rate of 25%. Prognosis, aside from liver fibrosis, usually depends on the status of the kidneys, CNS, heart, and gastrointestinal tract. The vascularity associated with these organs is affected and contributes heavily to the prognosis. Renal failure is shown to be higher in those with HCV compared to mixed cryoglobulinemia.

**EPIDEMIOLOGY**

Cryoglobulinemia is a rare condition and is clinically significant in about 1 in 100,000 individuals, with a higher prevalence observed in southern Europe. Cryoglobulins have been identified in several patient populations, specifically 15% to 20% of HIV-infected individuals, 40% to 65% of HCV-infected patients, and over 90% of HIV/HCV-coinfected individuals.

In addition, the condition is also linked to autoimmune diseases, such as SLE and Sjögren syndrome, as well as hematologic malignancies, such as multiple myeloma and lymphoma.

Cryoglobulinemia predominantly affects adults, with a higher incidence observed in females than males. Based on the currently available case series, patients with type 1 cryoglobulin account for 5% to 25% of the cases. Geographic variations in prevalence are noted, correlating with the distribution of HCV infection and other associated diseases. Due to its association with various underlying conditions, the epidemiology of cryoglobulinemia reflects a complex interplay between genetic, environmental, and infectious factors.

**REFERENCE**

[Cryoglobulinemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK557606/#article-20147.s10)

[Cryoglobulinemia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/cryoglobulinemia/symptoms-causes/syc-20371244)

[Cryoglobulinemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/cryoglobulinemia/diagnosis-treatment/drc-20449756)

**Antiphospholipid syndrome**

**DEFINITION AND DESCRIPTION**

This is a condition in which the immune system mistakenly creates antibodies that attack tissues in the body. These antibodies can cause blood clots to form in arteries and veins.

Blood clots can form in the legs, lungs and other organs, such as the kidneys and spleen. The clots can lead to a heart attack, strokes and other conditions. During pregnancy, antiphospholipid syndrome also can result in miscarriage and stillbirth. Some people who have the syndrome have no signs or symptoms.

There's no cure for this uncommon condition, but medications can reduce the risk of blood clots and miscarriage.

**CAUSES OF ANTIPHOSPHOLIPID SYNDROME**

Antiphospholipid syndrome occurs when the immune system mistakenly produces antibodies that make blood much more likely to clot. Antibodies usually protect the body against invaders, such as viruses and bacteria.

Antiphospholipid syndrome can be caused by an underlying condition, such as an autoimmune disorder. You can also develop the syndrome without an underlying cause.

**Risk Factor**

Antiphospholipid syndrome is more common in women than in men. Having another autoimmune condition, such as lupus, increases the risk of antiphospholipid syndrome.

It's possible to have the antibodies associated with antiphospholipid syndrome without developing signs or symptoms. However, having these antibodies increases your risk of developing blood clots, particularly if you:

* Become pregnant
* Are immobile for a time, such as being on bed rest or sitting during a long flight
* Have surgery
* Smoke cigarettes
* Take oral contraceptives or estrogen therapy for menopause
* Have high cholesterol and triglycerides levels

**SYMptoms OF ANTIPHOSPHOLIPID SYNDROME**

Signs and symptoms of antiphospholipid syndrome can include:

* **Blood clots in legs (DVT).** Signs of a deep vein thrombosis (DVT) include pain, swelling and redness. These clots can travel to the lungs (pulmonary embolism).
* **Repeated miscarriages or stillbirths.** Other complications of pregnancy include dangerously high blood pressure (preeclampsia) and premature delivery.
* **Stroke.** A stroke can occur in a young person who has antiphospholipid syndrome but no known risk factors for cardiovascular diseases.
* **Transient ischemic attack (TIA).** Similar to a stroke, a transient ischemic attack (TIA) usually lasts only a few minutes and causes no permanent damage.
* **Rash.** Some people develop a red rash with a lacy, net-like pattern.

Less common signs and symptoms include:

* **Neurological symptoms.** Chronic headaches, including migraines; dementia and seizures are possible when a blood clot blocks blood flow to parts of the brain.
* **Cardiovascular disease.** Antiphospholipid syndrome can damage heart valves.
* **Low blood platelet counts (thrombocytopenia).** This decrease in blood cells needed for clotting can cause episodes of bleeding, particularly from the nose and gums. Bleeding into the skin will appear as patches of small red spots.

## 

## Diagnosis and Test

If you've had episodes of blood clots or pregnancy loss that aren't explained by known health conditions, your health care provider can schedule blood tests to check for clotting and for the presence of the antibodies associated with antiphospholipid syndrome.

To confirm a diagnosis of antiphospholipid syndrome, the antibodies must appear in your blood at least twice, in tests conducted 12 or more weeks apart.

You can have antiphospholipid antibodies and never develop signs or symptoms. A diagnosis of antiphospholipid syndrome is made only when these antibodies cause health problems.

## 

## 

## Treatment

If you have blood clots, standard initial treatment involves a combination of blood-thinning medications. The most common are heparin and warfarin (Jantoven). Heparin is fast-acting and delivered via injections. Warfarin comes in pill form and takes several days to take effect. Aspirin is also a blood thinner.

When you're taking blood thinners, you have an increased risk of bleeding episodes. Your doctor will monitor your dosage with blood tests to be sure your blood is capable of clotting enough to stop the bleeding of a cut or the bleeding under the skin from a bruise.

There is some evidence that other drugs might be helpful in treating antiphospholipid syndrome. These include hydroxychloroquine (Plaquenil), rituximab (Rituxan) and statins. More study is needed.

### Treatment during pregnancy

It's possible to have a successful pregnancy if you have antiphospholipid syndrome, especially with treatment. Treatment usually involves heparin or heparin with aspirin. Warfarin isn't given to pregnant women because it can affect the fetus.

## 

## 

## Self care

Depending on your treatment plan for antiphospholipid syndrome, there are other steps you can take to protect your health. If you take blood-thinning medications, take extra care to keep from injuring yourself and to avoid bleeding.

* Avoid contact sports or other activities that could cause bruising or injury or cause you to fall.
* Use a soft toothbrush and waxed floss.
* Shave with an electric razor.
* Take extra care when using knives, scissors and other sharp tools.
* Women should avoid using estrogen therapy for contraception or menopause.

### Food and dietary supplements

Certain foods and medications may affect how well your blood thinners work. Ask your health care provider for guidance about:

* **Safe dietary choices.** Vitamin K can lessen the effectiveness of warfarin, but not other blood-thinners. You might need to avoid eating large amounts of vitamin K-rich foods such as avocado, broccoli, Brussels sprouts, cabbage, leafy greens and garbanzo beans. Alcohol can increase warfarin's blood-thinning effect. Ask your doctor if you need to limit or avoid alcohol.
* **Safe medications and dietary supplements.** Certain medications, vitamins and herbal products can interact dangerously with warfarin. These include some pain relievers, cold medicines, stomach remedies or multivitamins, as well as garlic, ginkgo and green tea.

## Complications

Complications of antiphospholipid syndrome can include:

* **Kidney failure.** This can result from decreased blood flow to your kidneys.
* **Stroke.** Decreased blood flow to a part of your brain can cause a stroke, which can result in permanent neurological damage, such as partial paralysis and loss of speech.
* **Cardiovascular problems.** A blood clot in your leg can damage the valves in the veins, which keep blood flowing to your heart. This can result in chronic swelling and discoloration in your lower legs. Another possible complication is heart damage.
* **Lung problems.** These can include high blood pressure in your lungs and pulmonary embolism.
* **Pregnancy complications.** These can include miscarriages, stillbirths, premature delivery, slow fetal growth and dangerously high blood pressure during pregnancy (preeclampsia).

Rarely, in severe cases, antiphospholipid syndrome can lead to multiple organ damage in a short time.

## When to see a doctor

Contact your health care provider if you have unexplained bleeding from your nose or gums; an unusually heavy menstrual period; vomit that is bright red or looks like coffee grounds; black, tarry stool or bright red stool; or unexplained abdominal pain.

Seek emergency care if you have signs and symptoms of:

* **Stroke.** A clot in your brain can cause sudden numbness, weakness or paralysis of your face, arm or leg. You may have difficulty speaking or understanding speech, visual disturbances and a severe headache.
* **Pulmonary embolism.** If a clot lodges in your lung, you may experience sudden shortness of breath, chest pain and coughing up blood-streaked mucus.
* **Deep vein thrombosis (DVT).** Signs and symptoms of DVTs include swelling, redness, or pain in a leg or arm.

**EPIDEMIOLOGY**

Estimating the frequency of APS has been challenging given the changes in the definition of the APS classification criteria, the lack of standardization to detect aPL, differences in laboratory cutoffs, and other difficulties such as confirming aPL positivity 12 weeks after the initial measurement.

The epidemiological data remains limited, but the characterization of the incidence and prevalence of APS in the general population has improved with several new publications in recent years. For this review and given the paucity of data, we included data presented in international conferences that has not been published yet. There have been six studies estimating the frequency of APS in the general population, one from the USA, one from South America, one from Asia, and three from Europe. The studies have used different methodologies or population samples, some relying on the use of diagnostic codes as case definition while others relied on medical record review and current classification criteria. Few studies have been population-based, while others have been based on regional registries or health management organizations.

**Differential Diagnosis**

## Diagnostic Considerations

Other problems to be considered in the differential diagnosis of antiphospholipid syndrome (APS) include the following:

* Hypercoagulable state: Malignancy, oral contraceptive use and hormone replacement therapy, homocystinemia, antithrombin III deficiency, protein C or S deficiency, factor V Leiden mutation, prothrombin A20210 mutation, antiprothrombin antibodies
* Atherosclerotic vascular disease, including multiple cholesterol emboli syndrome
* Systemic necrotizing vasculitis
* Infection: certain infections (eg, skin infections, pneumonia, urinary tract infections) may result in the formation of antiphospholipid antibodies without the development of antiphospholipid syndrome

The ACR/EULAR classification criteria comprise six clinical domains and two laboratory domains. A total of 3 points from clinical domains, along with 3 points from laboratory domains, are required to classify as APS.

*Clinical domains*

The clinical domains are as follows:

1. Macrovascular – venous thromboembolism (VTE)
2. Macrovascular – arterial thrombosis (AT)
3. Microvascular – other
4. Obstetric
5. Cardiac valve
6. Hematologic
7. Systemic Lupus Erythematosus (SLE)
   1. APS can occur as a primary disorder or secondary to SLE.
   2. Both share clinical features such as thrombosis and pregnancy loss.
   3. SLE is often accompanied by other autoantibodies (anti-dsDNA, anti-Sm), complement consumption, and multisystem involvement.
   4. Neuropsychiatric symptoms may overlap but require different treatment approaches.
8. Thrombotic Microangiopathies
   1. Thrombotic thrombocytopenic purpura (TTP)
   2. Hemolytic uremic syndrome (HUS)
   3. These cause microvascular thrombosis and organ damage but have distinct laboratory markers (e.g., ADAMTS13 deficiency in TTP) and clinical courses.
9. Vasculitis and Other Autoimmune Disorders
   1. Henoch-Schönlein purpura, polyarteritis nodosa, and other vasculitides can mimic APS with vascular inflammation and thrombosis.
   2. Clinical presentation and biopsy findings help differentiate.
10. Malignant Hypertension and Lupus Nephritis
    1. APS-associated nephropathy must be distinguished from these causes of kidney injury, often requiring renal biopsy.
11. Inherited or Acquired Thrombophilias
    1. Factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency, antithrombin deficiency.
    2. These cause thrombosis but lack the characteristic antiphospholipid antibodies.
12. Other Causes of Recurrent Pregnancy Loss
    1. Genetic abnormalities, uterine anomalies, hormonal imbalances, infections.
13. Seronegative APS
    1. Patients with clinical features of APS but negative standard antibody tests may require testing for non criteria antibodies.

References

[Epidemiology of Antiphospholipid Syndrome in the General Population - PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC8727975/#Sec2)

[Antiphospholipid syndrome - Symptoms & causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/antiphospholipid-syndrome/symptoms-causes/syc-20355831)

[Antiphospholipid syndrome - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/antiphospholipid-syndrome/diagnosis-treatment/drc-20355836)

[Antiphospholipid Syndrome Differential Diagnoses](https://emedicine.medscape.com/article/333221-differential?form=fpf)

**Hemochromatosis**

**Definition and description**

This 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.

**CAUSES OF HEMOCHROMATOSIS**

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.

**Symptoms of hemochromatosis**

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.

## Diagnosis and test

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 used in hemochromatosis.

**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.

**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.

### 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.

**PROGNOSIS**

If left untreated, hemochromatosis can lead to progressive liver damage and cirrhosis, hepatocellular carcinoma, and other complications associated with iron overload in the tissues and organs. The prognosis has improved in the last few decades with advances in diagnosis and management of this condition. Hepatic fibrosis or cirrhosis is the main prognostic indicator at the time of diagnosis. Early diagnosis and regular treatment with phlebotomy can decrease most of the complications associated with hemochromatosis.

**Differential Diagnosis**

Due to the involvement of multiple organ systems, several differential diagnoses must also be considered when evaluating patients with clinical features of hemochromatosis, including:

* 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

**EPIDEMIOLOGY**

Hereditary hemochromatosis is the most common autosomal recessive disorder in White populations, with a prevalence of 1 in 300 to 500 individuals. Hereditary hemochromatosis types 2, 3, and 4 are seen worldwide, but type 1 is primarily seen in people of northern European descent. The prevalence of hemochromatosis is the same in Europe, Australia, and other Western countries, with excess in people of Celtic or Scandinavian origin. Hemochromatosis is less prevalent in patients of African descent. White individuals have a 6 times higher risk of developing the disease than Black individuals.

In hemochromatosis, men are affected 2 to 3 times more often than women. The estimated ratio between men and women is 1.8:1 to 3:1. Women with hemochromatosis become symptomatic later in life than men due to the blood loss and consequent iron excretion associated with menstruation. The disease usually becomes apparent in men in the fifth decade; in women, it often presents in the sixth decade. In contrast, juvenile hemochromatosis may appear in persons aged 10 to 30. Analyses of a p.C282Y homozygous genotypic subset have revealed the greatest morbidity is in those patients older than 60. The main risk factors for hemochromatosis include:

* *C28Y* homozygosity (most significant risk factor)
* Positive family history
* Northern European heritage
* Male sex

REFERENCES

[Hemochromatosis - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK430862/#article-22724.s10)

[Hemochromatosis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hemochromatosis/diagnosis-treatment/drc-20351448)

[Hemochromatosis - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hemochromatosis/symptoms-causes/syc-20351443)

**AMYLOIDOSIS**

**Definition and description**

Amyloidosis (am-uh-loi-DO-sis) is a rare disease that occurs when a protein called amyloid builds up in organs. This amyloid buildup can make the organs not work properly.

Organs that may be affected include the heart, kidneys, liver, spleen, nervous system and digestive tract.

Some types of amyloidosis occur with other diseases. These types may improve with treatment of the other diseases. Some types of amyloidosis may lead to life-threatening organ failure.

Treatments may include chemotherapy with strong drugs used to treat cancer. Other types of medications can reduce amyloid production and control symptoms. Some people may benefit from organ or stem cell transplants.

You may not experience symptoms of amyloidosis until later in the course of the disease. Symptoms may vary, depending on which organs are affected.

**Causes of amyloidosis**

There are many different types of amyloidosis. Some types are hereditary. Others are caused by outside factors, such as inflammatory diseases or long-term dialysis. Many types affect multiple organs. Others affect only one part of the body.

Types of amyloidosis include:

* **AL amyloidosis (immunoglobulin light chain amyloidosis).** This is the most common type of amyloidosis in developed countries. AL amyloidosis is also called primary amyloidosis. It usually affects the heart, kidneys, liver and nerves.
* **AA amyloidosis.** This type is also known as secondary amyloidosis. It's usually triggered by an inflammatory disease, such as rheumatoid arthritis. It most commonly affects the kidneys, liver and spleen.
* **Hereditary amyloidosis (familial amyloidosis).** This inherited disorder often affects the nerves, heart and kidneys. It most commonly happens when a protein made by your liver is abnormal. This protein is called transthyretin (TTR).
* **Wild-type amyloidosis.** This variety has also been called senile systemic amyloidosis. It occurs when the TTR protein made by the liver is normal but produces amyloid for unknown reasons. Wild-type amyloidosis tends to affect men over age 70 and often targets the heart. It can also cause carpal tunnel syndrome.
* **Localized amyloidosis.** This type of amyloidosis often has a better prognosis than the varieties that affect multiple organ systems. Typical sites for localized amyloidosis include the bladder, skin, throat or lungs. Correct diagnosis is important so that treatments that affect the entire body can be avoided.

**Risk factors**

Factors that increase the risk of amyloidosis include:

* **Age.** Most people diagnosed with amyloidosis are between ages 60 and 70.
* **Sex.** Amyloidosis occurs more commonly in men.
* **Other diseases.** Having a chronic infectious or inflammatory disease increases the risk of AA amyloidosis.
* **Family history.** Some types of amyloidosis are hereditary.
* **Kidney dialysis.** Dialysis can't always remove large proteins from the blood. If you're on dialysis, abnormal proteins can build up in your blood and eventually be deposited in tissue. This condition is less common with more modern dialysis techniques.
* **Race.** People of African descent appear to be at higher risk of carrying a genetic mutation associated with a type of amyloidosis that can harm the heart.

**SYMPTOMS OF AMYLOIDOSIS**

Signs and symptoms of amyloidosis may include:

* Severe fatigue and weakness
* Shortness of breath
* Numbness, tingling, or pain in the hands or feet
* Swelling of the ankles and legs
* Diarrhea, possibly with blood, or constipation
* An enlarged tongue, which sometimes looks rippled around its edge
* Skin changes, such as thickening or easy bruising, and purplish patches around the eyes

## 

## Diagnosis and test

Amyloidosis is often overlooked because the signs and symptoms can mimic those of more-common diseases.

Early diagnosis can help prevent further organ damage. Precise diagnosis is important because treatment varies greatly, depending on your specific condition.

### Laboratory tests

Blood and urine may be analyzed for abnormal protein that can indicate amyloidosis. People with certain symptoms may also need thyroid and kidney function tests.

### Biopsy

A tissue sample can be checked for signs of amyloidosis. The biopsy may be taken from the fat under the skin on the abdomen or from bone marrow. Some people may need a biopsy of an affected organ, such as the liver or kidney. The tissue can be tested to see what type of amyloid is involved.

### Imaging tests

Images of the organs affected by amyloidosis may include:

* **Echocardiogram.** This technology uses sound waves to create moving images that can show how well the heart is working. It can also show heart damage that can be specific to particular types of amyloidosis.
* **Magnetic resonance imaging (MRI).** MRI uses radio waves and a strong magnetic field to create detailed images of organs and tissues. These can be used to check the structure and function of the heart.
* **Nuclear imaging.** In this test, tiny amounts of radioactive material (tracers) are injected into a vein. This can reveal early heart damage caused by certain types of amyloidosis. It can also help distinguish between different types of amyloidosis, which can guide treatment decisions.

## Treatment

There's no cure for amyloidosis. But treatment can help manage signs and symptoms and limit further production of amyloid protein. If the amyloidosis has been triggered by another condition, such as rheumatoid arthritis or tuberculosis, treating the underlying condition can be helpful.

### Medications

* **Chemotherapy.** Some cancer drugs are used in AL amyloidosis to stop the growth of abnormal cells that produce the protein that forms amyloid.
* **Heart medications.** If your heart is affected, you may need to take blood thinners to reduce the risk of clots. You may also need medications to control your heart rate. Drugs that increase urination can reduce the strain on your heart and kidneys.
* **Targeted therapies.** For certain types of amyloidosis, drugs such as patisiran (Onpattro) and inotersen (Tegsedi) can interfere with the commands sent by faulty genes that create amyloid. Other drugs, such as tafamidis (Vyndamax, Vyndaqel) and diflunisal, can stabilize bits of protein in the bloodstream and prevent them from getting transformed into amyloid deposits.

### Surgical and other procedures

* **Autologous blood stem cell transplant.** This procedure involves collecting your own stem cells from your blood through a vein and storing them for a short time while you have high-dose chemotherapy. The stem cells are then returned to your body via a vein. This treatment is most appropriate for people whose disease isn't advanced and whose heart isn't greatly affected.
* **Dialysis.** If your kidneys have been damaged by amyloidosis, you may need to start dialysis. This procedure uses a machine to filter wastes, salts and fluid from your blood on a regular schedule.
* **Organ transplant.** If amyloid deposits have severely damaged your heart or kidneys, you might need surgery to replace those organs. Some types of amyloid are formed in the liver, so a liver transplant could stop that production.

### When to see a doctor

See your health care provider if you regularly experience any of the signs or symptoms associated with amyloidosis.

**Complications of amyloidosis**

Amyloidosis can seriously damage the:

* **Heart.** Amyloid reduces the heart's ability to fill with blood between heartbeats. Less blood is pumped with each beat. This can cause shortness of breath. If amyloidosis affects the heart's electrical system, it can cause heart rhythm problems. Amyloid-related heart problems can become life-threatening.
* **Kidneys.** Amyloid can harm the kidneys' filtering system. This affects their ability to remove waste products from the body. It can eventually cause kidney failure.
* **Nervous system.** Nerve damage can cause pain, numbness, or tingling of the fingers and feet. If amyloid affects the nerves that control bowel function, it can cause periods of alternating constipation and diarrhea. Damage to the nerves that control blood pressure can make people feel faint if they stand up too quickly.

**Epidemiology of Amyloidosis**

* AL (Light-Chain) Amyloidosis:
  + Global incidence is estimated between 3 to 16.7 cases per million persons per year, with most studies reporting around 9 to 14 cases per million annually.
  + Prevalence in the United States is estimated at 30,000 to 45,000 patients, with about 12,000 adults currently living with AL amyloidosis.
  + The prevalence increased significantly from 15.5 per million in 2007 to 40.5 per million in 2015 in the US, while incidence rates remained relatively stable.
  + AL amyloidosis is more common in males and predominantly affects individuals over 65 years of age.
  + Incidence rates vary by region but show no significant geographic variation within the US.
  + In Asia (Taiwan), incidence rates are lower, around 5.3 to 6.6 per million population, increasing with age.
* Hereditary ATTR (ATTRv) Amyloidosis:
  + Estimated global prevalence is approximately 1 in 450,000 people (range 1 in 120,000 to 1 in 830,000), making it much rarer than AL amyloidosis.
* Cardiac Amyloidosis:
  + Estimated annual incidence in the US is about 2,500 to 5,000 new cases per year.
  + Hospitalization-based studies estimate a 10-year period prevalence of about 125 cases per million people

**Differential Diagnosis**

## General Differential Diagnosis for Amyloidosis

* Other systemic diseases with similar symptoms:
  + Acute myocarditis
  + Bronchiectasis
  + Multiple myeloma and other monoclonal gammopathies
  + Collagen vascular diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus)
  + Familial Mediterranean fever
  + Tuberculosis
  + Ulcerative colitis
  + Vitamin deficiencies (e.g., B12)
  + Drug or toxic nephropathy
  + Glomerulonephritis
  + Nephrotic syndrome
  + Peripheral neuropathy from other causes
  + Osteomyelitis
  + Rheumatoid polyarteritis
  + Leprosy
  + Hemodialysis-related amyloidosis
* Infiltrative cardiomyopathies mimicking cardiac amyloidosis:
  + Glycogen storage diseases
  + Fabry disease
  + Hurler syndrome
  + Restrictive cardiomyopathy of other etiologies
  + Myocardial fibrosis
* Other causes of renal disease:
  + Familial renal amyloidosis
  + Membranous glomerulonephritis
  + Renal vein thrombosis
* Cutaneous amyloidosis differential:
  + Other skin conditions with similar lesions (not detailed here but includes various dermatologic disorders)

Differential Diagnosis by Amyloidosis Type and Organ Involvement

AL (Primary) Amyloidosis:

* Multiple myeloma
* Other plasma cell dyscrasias
* Chronic inflammatory diseases (for AA amyloidosis)
* Familial amyloidosis variants

AA (Secondary) Amyloidosis:

* Chronic inflammatory or infectious diseases (e.g., rheumatoid arthritis, Crohn’s disease)

ATTR (Transthyretin) Amyloidosis:

* Other causes of restrictive cardiomyopathy
* Hypertrophic cardiomyopathy
* Senile systemic amyloidosis (wild-type ATTR)
* Hereditary neuropathies

REFERENCES

[Amyloidosis - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/amyloidosis/diagnosis-treatment/drc-20353183)

[Amyloidosis - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/amyloidosis/symptoms-causes/syc-20353178)

**CASTLEMAN DISEASE**

**DEFINITION AND DESCRIPTION**

Castleman disease is a group of rare disorders that involves lymph nodes that get bigger, called enlarged lymph nodes, and a wide range of symptoms. The most common form of the disorder involves a single enlarged lymph node. This lymph node is usually in the chest or neck, but it can occur in other areas of the body as well. This form of the disorder is called unicentric Castleman disease (UCD).

Multicentric Castleman disease (MCD) involves multiple regions of enlarged lymph nodes, inflammatory symptoms and problems with organ function. There are three types of MCD:

* **HHV-8-associated MCD.** This type is linked to human herpes virus type 8, called HHV-8, and human immunodeficiency virus (HIV).
* **Idiopathic MCD.** The cause of this type is unknown. This also is called HHV-8-negative MCD.  
  The most serious form of this type of MCD is known as iMCD-TAFRO. This condition gets its name from the symptoms it causes.
* **POEMS-associated MCD.** This type is linked to another condition called POEMS syndrome. POEMS syndrome is a rare blood disorder that damages nerves and affects other parts of the body.

Sometimes, people may have 2-3 enlarged lymph nodes and mild symptoms that do not meet the diagnostic criteria for MCD. These people may have another disease, or they may have the recently described subtype of Castleman disease called oligocentric Castleman disease. This subtype is rare.

Treatment and outlook vary depending on the type of Castleman disease you have. Unicentric Castleman disease, which is the type that involves only one enlarged lymph node, can usually be successfully treated with surgery.

The best treatment for oligocentric Castleman disease, which involves a few enlarged lymph nodes and has limited symptoms, is not known but is thought to be similar to the treatment for unicentric Castleman disease.

While not all people with MCD respond to the first treatment, there are medicines that work to treat HHV-8-associated MCD and idiopathic MCD.

**Symptoms of castleman disease**

Many people with unicentric Castleman disease don't notice any signs or symptoms. The enlarged lymph node may be found during a physical exam or an imaging test for a different problem.

Some people with unicentric Castleman disease might have signs and symptoms that are more often seen in multicentric Castleman disease. These may include:

### Body symptoms

* Fever.
* Weight loss that happens without trying.
* Fatigue.
* Night sweats.
* Swelling.
* Enlarged liver or spleen.

### Blood symptoms

* Low red blood cell count, also called anemia.
* High or low platelet counts.
* Higher creatinine levels that happen because the kidneys don't work properly.
* Higher levels of antibodies known as immunoglobulins.
* Low levels of a blood protein called albumin.

Symptoms of the more serious form of idiopathic MCD called iMCD-TAFRO are:

* Low platelet count, also called thrombocytopenia.
* Swelling and fluid in the body, known as anasarca.
* Fever or a higher level of C-reactive protein, a marker of inflammation.
* Reticulin fibrosis, which is checked by taking a sample of bone marrow.
* Organ swelling, also called organomegaly.

### When to see a doctor

If you notice an enlarged lymph node on the side of your neck or in your underarm, collarbone or groin area, talk with your healthcare professional. Also call your care team if you have a lasting feeling of fullness in your chest or abdomen, fever, fatigue, or weight loss that you can't explain.

**Causes of castleman disease**

It's not clear what causes unicentric Castleman disease or idiopathic multicentric Castleman disease (MCD). However, HHV-8-positive MCD is known to occur in people who don't have typical function in their immune systems because of HIV or other causes.

**Risk factors**

Castleman disease can affect people of any age or gender. People usually are diagnosed with Castleman disease during midlife, but it can happen at any age, including during childhood.

There are no known risk factors for unicentric Castleman disease or idiopathic multicentric Castleman disease. Infection with HIV or having a condition that decreases how well the immune system works raises the risk of having HHV-8-positive multicentric Castleman disease.

## Diagnosis and test

After reviewing your medical history and doing a detailed physical exam, your healthcare professional may recommend:

* **Blood and urine tests.** These help rule out other infections or diseases. These tests also can find anemia and changes in blood proteins that can be typical of Castleman disease.
* **Imaging tests.** These tests can find enlarged lymph nodes or an enlarged liver or spleen. A CT scan of the neck, chest, abdomen and pelvis may be used. A positron emission tomography scan, also known as a PET scan, may be used to diagnose Castleman disease. PET scans also can show whether a treatment is working.
* **Lymph node biopsy.** This test is essential to diagnose Castleman disease and rule out related disorders, such as lymphoma. In a biopsy, a tissue sample from an enlarged lymph node is removed and looked at in a laboratory.

## Treatment

Treatment depends on the type of Castleman disease you have.

### Unicentric Castleman disease

Surgery to remove the affected lymph node is the usual treatment for unicentric Castleman disease (UCD). If the lymph node is in the chest or abdomen, major surgery may be needed.

Surgery to remove the enlarged lymph node usually cures UCD. However, UCD sometimes comes back. If surgery is not possible, you may need medicines typically used for multicentric Castleman disease. If medicines don't work, radiation therapy may be an option.

More research into the treatment of oligocentric Castleman disease is needed, but treatment is usually similar to that of UCD.

You'll likely need follow-up exams, including imaging and laboratory tests, to check that the disease hasn't come back.

### HHV-8-positive multicentric Castleman disease

Rituximab (Rituxan) is usually the first treatment for HHV-8-positive MCD. Rituximab is highly effective, but sometimes medicines called antivirals and chemotherapies are needed. Antiviral medicines can block the activity of HHV-8 or HIV, and chemotherapies can get rid of extra immune cells.

### Idiopathic multicentric Castleman disease

Siltuximab (Sylvant) is usually the first treatment for idiopathic MCD. In the U.S., siltuximab is the only medicine approved by the Food and Drug Administration (FDA) for the treatment of idiopathic MCD. People who get better after taking siltuximab tend to have successful long-term treatment. This drug blocks the action of a protein called interleukin-6. The bodies of people who have idiopathic MCD produce too much of this protein.

People who are critically ill with idiopathic MCD often receive treatment with medicines called corticosteroids. They also may need chemotherapy. Corticosteroids such as prednisone can help control inflammation. Chemotherapy can get rid of immune cells that are causing problems.

When siltuximab doesn't work, other treatments such as rituximab (Rituxan) and sirolimus (Rapamune) may be used.

**Complications**

People with unicentric Castleman disease (UCD) usually do well once the affected lymph node is removed, and life expectancy is usually not changed. But they are at increased risk of developing a rare autoimmune condition called paraneoplastic pemphigus. This condition can be life-threatening. Paraneoplastic pemphigus causes blisters in the mouth and on the skin that are often misdiagnosed. Though the risk of developing paraneoplastic pemphigus is low, being checked for this condition is important if you have UCD.

Idiopathic multicentric Castleman disease can rapidly get worse to involve life-threatening problems with organ function. This requires critical care with a machine that helps with breathing, called a ventilator, and treatments that help with organ function, such as dialysis and transfusions.

HHV-8-positive multicentric Castleman disease may involve life-threatening infections and organ failure. People who also have HIV/AIDS generally have worse outcomes.

**PROGNOSIS**

UCD being able to be eliminated with surgical resection has a good prognosis. However, since multiple systemic disorders involve MCD and sometimes concomitant diseases like HIV and HHV-8 can also be present, specific chemotherapy regimens have not been assigned, and better treatment methods still need to be explored. Moreover, along with the deficient treatment options, nonspecific clinical features that often go unnoticed with limited diagnostic measures also lead to delayed confirmation of its diagnosis. Its prognosis is, therefore, abysmal.

Both UCD and MCD can sometimes progress to non-Hodgkin lymphoma (NHL)

**DIFFERENTIAL DIAGNOSIS**

Castleman disease is easily confused with lymphoma or other solid tumors. Therefore, it is essential to properly diagnose the exact type of CD and distinguish it from other diseases by clinical history and laboratory diagnostic measures with additional imaging techniques for prompt treatment and management procedures. Even though CD was defined as a benign lymphoproliferative disease, the systemic forms are particularly associated with related neoplasms and autoimmune disorders like Kaposi sarcoma and Follicular dendritic cell (FDC) tumors.Lymphomas, especially Hodgkin and angioimmunoblastic T-cell lymphoma, are also known for polymorphous infiltrate and hypervascularity, are well-known to mimic Castleman disease.

The hyaline vascular CD can be strongly connected to FDC tumors, including dendritic cell sarcomas and neoplasms of the stroma. In addition, IL-6 release in CD may invoke molecular mimicry and epitope spreading, initiating a lichenoid interface dermatitis, leading to autoantibody production. Finally, it can be associated with a fatal autoimmune blistering disease called paraneoplastic pemphigus in patients with treatment-resistant erosive mucosal lesions.

POEMS syndrome is characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes and is a rare plasma cell disease with multisystem involvement. Around 30% of patients with POEMS disease also have multicentric CD, more precisely the HHV-8 positive variant. In addition, many findings of systemic CD-like ascites, lymphadenopathy, hepatosplenomegaly, and polyneuropathy overlap POEMS syndrome.

The HHV-8 associated CD and Kaposi sarcoma are vascular lesions caused by the same viral agent, HHV-8. Therefore, they frequently appear alongside HIV as well.

Some IgG4-related diseases like sclerosing cholangitis, Kuttner tumor, retroperitoneal fibrosis, Mikulicz disease, autoimmune pancreatitis are associated with hypertrophy of lymph nodes, similar to that in multicentric CD. However, these two diseases can be differentiated based on laboratory findings, i.e., raised serum IgG4 levels and IgG4-positive plasma infiltrates in the IgG4-related diseases and IL-6 elevation in Castleman disease.

**EPIDEMIOLOGY**

The lack of proper knowledge and even a formal definition of Castleman disease made it challenging to assess its epidemiology. A study was conducted in 2008 by Simpson which showed that:

* The incidence of UCD is 16 per million patient-years and affects all age groups.
* The incidence of HHV-8 associated CD varies widely, but it is more common in HIV-positive men.
* The incidence of iMCD is 5 per million patient-years.

Another study conducted in the US from 2000 to 2009 concluded that out of 59 patients with MCD, 61% were males with the mean age of 53 years, and 68% were white.

The hyaline-vascular variant is more common than the plasma-cell type, comprising 91% of the total cases.

Its predominance in any specific sex or race is not noted. Castleman disease usually develops in most patients before reaching 30, although the age range is broad.

REFERENCES

[Castleman Disease - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK576394/#article-135910.s11)

[Castleman disease - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/castleman-disease/diagnosis-treatment/drc-20543055)

[Castleman disease - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/castleman-disease/symptoms-causes/syc-20543017)

**HYPEREOSINOPHILIC SYNDROME**

**DEFINITION AND DESCRIPTION**

Hypereosinophilic (hy-per-ee-o-SIN-o-phil-ik) syndrome (HES) is a group of blood disorders that occur when you have high numbers of eosinophils — white blood cells that play an important role in your immune system. Over time, the excess eosinophils enter various tissues, eventually damaging your organs.

The most common targets are the skin, lungs, digestive tract, heart, blood and nervous system. Untreated, HES can become life-threatening.

**Symptoms of hypereosinophilic syndrome**

Early symptoms of HES may include fatigue, cough, breathlessness, muscle pain, rash and fever.

**Causes**

Some varieties of hypereosinophilic syndrome tend to run in families. Other types have been associated with certain types of cancers, infections or other health problems.

**Risk factors**

HES can affect anyone. But it occurs more often in men, usually between the ages of 20 and 50.

## Diagnosis and test

Many types of disorders can raise your eosinophil level, including certain infections, allergies and reactions to medications. When trying to determine whether you have hypereosinophilic syndrome (HES), your doctor is likely to ask about your travel history and any medications you're taking, to help rule out these other causes.

### Laboratory tests

Your doctor may also need information from some of the following lab tests:

* **Blood tests,** to detect autoimmune conditions, parasitic infections, or problems with your liver or kidneys
* **Allergy tests,** to detect environmental or food allergies
* **Stool tests,** to detect parasitic infections such as hookworm
* **Genetic test,** to check for a gene mutation that can cause HES

### Imaging tests

Imaging tests may include:

* **X-rays,** to check the condition of your lungs
* **CT scan,** to detect problems in the chest, abdomen and pelvis
* **Echocardiogram or MRI,** to assess heart function

## Treatment

Treatment for hypereosinophilic syndrome is aimed at reducing your eosinophil count to prevent tissue damage, especially to your heart. Specific treatment depends on your symptoms, the severity of your condition and the cause of your HES.

If you have no symptoms and your eosinophil count is low enough, you might require no treatment other than close monitoring for any changes related to HES.

### Medications

Systemic corticosteroids, such as prednisone, are the first line treatment. Other treatment options include:

* Hydroxyurea (Droxia, Hydrea, Siklos)
* Imatinib (Gleevec)
* Vincristine

Because HES can increase your risk of blood clots, you might also be prescribed blood-thinning medications such as warfarin (Coumadin).

### Surgery and other procedures

If nothing else has worked, your doctor might suggest a stem cell or bone marrow transplant.

## Prognosis

## While specific prognostic markers for patients with HES are not well-established, the prognosis varies widely. It spans from mildly symptomatic cases, manageable through observation and follow-up, to severe disease resulting in the development of fatal, end-organ damage such as leukemia or irreversible heart failure.

## In recent years, the prognosis of HES has improved, secondary to advancements in the earlier detection of complications, enhanced surgical management of cardiac involvement, and a broader array of therapeutic modalities targeting the underlying cause of HES.

## Further studies regarding the pathophysiology of different disease variants hold promise for refining therapeutic strategies and enhancing a favorable prognosis.

## Complications

## Complications of HES are attributed to the type and degree of end-organ involvement. The most fatal complications are leukemias, irreversible heart failure, endocarditis, and severe restrictive cardiomyopathy, causing ventricular arrhythmia due to alterations in the cardiac conducting system.

## **DIFFERENTIAL DIAGNOSIS**

## The differential diagnosis of HES varies depending on the extent of eosinophilia.

## In mild to moderate eosinophilia cases, consideration is given to reactive eosinophilia attributed to infectious and parasitic diseases. This possibility requires a meticulous evaluation, a detailed history and examination, and testing for ova, parasites, and helminth infections. It is important to rule out drugs or natural supplements as primary etiologies.

## In cases of more moderate to severe manifestations of HES, hematologic and other neoplastic diseases should be considered. Acute eosinophilic leukemia presents an increased number of immature eosinophils in the peripheral blood, bone marrow, or tissues, accompanied by more than 10% blasts in the marrow, distinguishing it from HES. Chronic myeloid leukemia is another diagnosis that may be differentiated from HES as it typically does not cause clinical complications of eosinophilia and can be identified by the detection of BCR:ABL fusion mRNA.

## Systemic mastocytosis with eosinophilia is a relevant differential diagnosis characterized by its association with D816V mutations in the KIT gene. Notably, systemic mastocytosis with eosinophilia has an equal sex distribution compared to HES, which is more predominant in men. Moreover, the ratio of absolute eosinophil count (AEC) to serum total tryptase (AEC/tryptase) is <100 in systemic mastocytosis with eosinophilia vs >100 in HES.

## Another crucial differential in the diagnostic workup of HES is eosinophilic granulomatosis with polyangiitis (EGPA). The key distinguishing factor between HES and EGPA is the presence of vasculitis in the latter.

**EPIDEMIOLOGY**

The true incidence and prevalence of hypereosinophilic syndromes is unknown. A 2010 study utilizing the Surveillance, Epidemiology, and End Results (SEER) database showed an estimated age-adjusted incidence rate between 0.16 and 0.36 per 100,000 and prevalence (calculated as a product of incidence times duration of chronic disease) between 0.36 to 6.3 per 100,000.

While HES occurs more commonly between the ages of 20 to 50, some pediatric cases are reported. Studies suggest that the frequencies of HES variants are similar between children and adults. Children with primary immunodeficiency are more commonly present with secondary HES than adults. In addition, children were noted to have higher median peak absolute eosinophil count, more gastrointestinal complaints, and less pulmonary involvement.

REFERENCES

[Hypereosinophilic Syndrome - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK599558/#article-149474.s10)

[Hypereosinophilic syndrome - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hypereosinophilic-syndrome/diagnosis-treatment/drc-20352856)

[Hypereosinophilic syndrome - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hypereosinophilic-syndrome/symptoms-causes/syc-20352854)

### Large granular lymphocytic leukemia (LGL)

**DEFINITION AND DESCRIPTION**

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.

## Symptoms

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.

### causes of 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.

### Differential Diagnosis

#### Reactive LGL proliferation.

Many conditions can lead to the development of reactive LGL proliferation, including splenectomy, solid organ or bone marrow graft, viral infections (human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus), solid tumor, and non-Hodgkin lymphoma. LGL proliferations are typically poly- or oligoclonal, last only several months, and are not responsible for cytopenias. In difficult cases, bone marrow biopsy could help because in reactive LGL proliferation, bone marrow infiltration is absent.

#### Bone marrow failure syndromes.

Bone marrow failure syndromes (aplastic anemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndrome [MDS]) are occasionally associated with LGL leukemia. STAT3 mutation was found in few patients with aplastic anemia and MDS with concomitant LGL leukemia, suggesting similar pathogenesis. In this series, STAT-3-mutated patients with aplastic anemia were more sensitive to immunosuppressive therapies, and STAT-3-mutated patients with MDS harbored a lower degree of bone marrow cellularity. Efficacy of immunosuppressive treatments directed against T lymphocyte–mediated immune response is a strong argument for a common role of autoreactive T cells in all of these diseases. Moreover, concurrent STAT3, DNMT3A, and TET2 mutations were found in a patient with T-LGL without MDS morphologic abnormalities, and those mutations were restricted to CD3+ T cells. The two latter mutations are recurrent mutations usually found in MDS.

A recent study revealed several cases of unexplained cytopenia in which STAT3 mutation status could after all correct the diagnosis. Those cases were classified as MDS without typical bone marrow dysplasia nor MDS typical mutation using next-generation sequencing analysis. This review suggests that it could be useful to add the Stat3 SH2 domain to the myeloid next-generation sequencing panel.

**EPIDEMIOLOGY**

LGL leukemia is a rare disorder constituting 2-5% of all chronic lymphoproliferative diseases in the US and Europe and 5-6% of all cases in the Asian population . Recent demographic studies of European and North American cohorts place the average incidence of LGL leukemia at 0.2-0.72 per million persons per year.

The incidence is approximately the same in both males and females. The median age at presentation is the middle age group (55-60 years) and it is less common in pediatric age groups. The aggressive variant is more common in the Asian continent. Females are diagnosed at a younger age compared with males. In a US-based population study, 14% of patients were under the age of 50 years at the time of diagnosis, in contrast to another French registry database that reported 26% patients <50 years of age.

The affiliation of LGL leukemia with autoimmune diseases creates a hindrance in the interpretation of the actual incidence of this leukemia as many patients have already received steroids and/or immunosuppressive therapies for the primary autoimmune diseases diagnosed before, concurrently, or after the diagnosis of the LGL leukemia. Nevertheless, certain ethnicities notably Asians of Japanese, Koreans, and Taiwanese descent have established predilection towards the form of Aggressive NK cell-leukemia. No definite sex predilection is found within these ethnic populations. However, the age group affected is younger, earlier by a decade or two from the other spectrum of LGL leukemia.

REFERENCE

[Large granular lymphocytic leukemia: a brief review - PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC8918699/#sec2)

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

## Common Blood Cancers

Blood cancers, or hematologic malignancies, arise from uncontrolled growth of abnormal blood cells, typically in the bone marrow, disrupting normal blood functions. Below are the primary types, their characteristics, and management strategies.

### Leukemia

**Definition and description**

Leukemia is a cancer of the blood and bone marrow marked by excessive production of abnormal white blood cells that fail to fight infections and crowd out normal blood cells

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system.

Many types of leukemia exist. Some forms of leukemia are more common in children. Other forms of leukemia occur mostly in adults.

Leukemia usually involves the white blood cells. Your white blood cells are potent infection fighters — they normally grow and divide in an orderly way, as your body needs them. But in people with leukemia, the bone marrow produces an excessive amount of abnormal white blood cells, which don't function properly.

Treatment for leukemia can be complex — depending on the type of leukemia and other factors. But there are strategies and resources that can help make your treatment successful.

**leukemia**, a cancer of the blood-forming tissues characterized by a large increase in the numbers of white blood cells (leukocytes) in the circulation or bone marrow. A number of different leukemias are classified according to the course of the disease and the predominant type of white blood cell involved. Some types of leukemia have been related to radiation exposure, as noted in the Japanese population exposed to the first atomic bomb at Hiroshima; other evidence suggests hereditary susceptibility.

Leukemias are defined as either acute or chronic and as either myelogenous (from bone marrow) or lymphocytic (involving lymphocytes). These characteristics are used to designate almost all cases as one of four types—acute myelogenous, acute lymphocytic, chronic myelogenous, and chronic lymphocytic leukemia. Acute leukemias affect immature cells; the disease develops rapidly, with symptoms including anemia, fever, bleeding, and swelling of the lymph nodes. Immature leukemia cells continue to divide in the bone marrow, which leads to rapid death if left untreated. In chronic leukemia the cells develop and are transported to the tissues, but the cells do not function normally. Myelogenous leukemia affects granulocytes and monocytes, white blood cells that destroy bacteria and some parasites.

The most common form in children, acute lymphocytic leukemia, once killed more than 90 percent of its victims within six months. With new drug therapies, the majority of acute lymphocytic patients now achieve complete remission, with no evidence of malignant cells in the blood. With continued therapy, more than half remain free of disease for five years or longer. These patients are presumed to be cured.

The disease is characterized by the uncontrolled growth of blood cells, usually white blood cells in the bone marrow. White blood cells are a fundamental component of the body’s immune response. Leukemia cells crowd out and replace normal blood and marrow cells.

The exact cause of leukemia isn’t known, but researchers believe the disease develops due to mutations in the DNA of certain blood cells, caused by other genetic or environmental factors.

Although many types of leukemia exist, some affect adults more commonly than others.

**Symptoms of leukemia**

Leukemia symptoms vary, depending on the type of leukemia. Common leukemia signs and symptoms include:

* Fever or chills
* Persistent fatigue, weakness
* Frequent or severe infections
* Losing weight without trying
* Swollen lymph nodes, enlarged liver or spleen
* Easy bleeding or bruising
* Recurrent nosebleeds
* Tiny red spots in your skin (petechiae)
* Excessive sweating, especially at night
* Bone pain or tenderness

### 

### When to see a doctor

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

Leukemia symptoms are often vague and not specific. You may overlook early leukemia symptoms because they may resemble symptoms of the flu and other common illnesses.

Sometimes leukemia is discovered during blood tests for some other condition.

Scientists don't understand the exact causes of leukemia. It seems to develop from a combination of genetic and environmental factors.

### How leukemia forms

In general, leukemia is thought to occur when some blood cells acquire changes (mutations) in their genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In leukemia, the mutations tell the blood cells to continue growing and dividing.

When this happens, blood cell production becomes out of control. Over time, these abnormal cells can crowd out healthy blood cells in the bone marrow, leading to fewer healthy white blood cells, red blood cells and platelets, causing the signs and symptoms of leukemia.

### How leukemia is classified

Doctors classify leukemia based on its speed of progression and the type of cells involved.

The first type of classification is by how fast the leukemia progresses:

* **Acute leukemia.** In acute leukemia, the abnormal blood cells are immature blood cells (blasts). They can't carry out their normal functions, and they multiply rapidly, so the disease worsens quickly. Acute leukemia requires aggressive, timely treatment.
* **Chronic leukemia.** There are many types of chronic leukemias. Some produce too many cells and some cause too few cells to be produced. Chronic leukemia involves more-mature blood cells. These blood cells replicate or accumulate more slowly and can function normally for a period of time. Some forms of chronic leukemia initially produce no early symptoms and can go unnoticed or undiagnosed for years.

The second type of classification is by type of white blood cell affected:

* **Lymphocytic leukemia.** This type of leukemia affects the lymphoid cells (lymphocytes), which form lymphoid or lymphatic tissue. Lymphatic tissue makes up your immune system.
* **Myelogenous (my-uh-LOJ-uh-nus) leukemia.** This type of leukemia affects the myeloid cells. Myeloid cells give rise to red blood cells, white blood cells and platelet-producing cells.

### Types of leukemia

The major types of leukemia are:

* **Acute lymphocytic leukemia (ALL).** This is the most common type of leukemia in young children. ALL can also occur in adults.
* **Acute myelogenous leukemia (AML).** AML is a common type of leukemia. It occurs in children and adults. AML is the most common type of acute leukemia in adults.
* **Chronic lymphocytic leukemia (CLL).** With CLL, the most common chronic adult leukemia, you may feel well for years without needing treatment.
* **Chronic myelogenous leukemia (CML).** This type of leukemia mainly affects adults. A person with CML may have few or no symptoms for months or years before entering a phase in which the leukemia cells grow more quickly.
* **Other types.** Other, rarer types of leukemia exist, including hairy cell leukemia, myelodysplastic syndromes and myeloproliferative disorders.

## Risk factors

Factors that may increase your risk of developing some types of leukemia include:

* Previous cancer treatment. People who've had certain types of chemotherapy and radiation therapy for other cancers have an increased risk of developing certain types of leukemia.
* Genetic disorders. Genetic abnormalities seem to play a role in the development of leukemia. Certain genetic disorders, such as Down syndrome, are associated with an increased risk of leukemia.
* Exposure to certain chemicals. Exposure to certain chemicals, such as benzene — which is found in gasoline and is used by the chemical industry — is linked to an increased risk of some kinds of leukemia.
* Smoking. Smoking cigarettes increases the risk of acute myelogenous leukemia.
* Family history of leukemia. If members of your family have been diagnosed with leukemia, your risk of the disease may be increased.

However, most people with known risk factors don't get leukemia. And many people with leukemia have none of these risk factors.

### Most forms of leukemia develop when immature white blood cells, red blood cells or platelets grow out of control, taking up space where healthy blood cells should exist. The disease develops when genetic mutations or damage occur in bone marrow tissue, which is responsible for making blood cells. There are four main types of leukemia:

* Acute lymphocytic leukemia (ALL) affects a type of white blood cell called lymphocytes
* Acute myeloid leukemia (AML) affects red blood cells, platelets and a type of white blood cell called myeloblasts
* Chronic lymphocytic leukemia (CLL) affects lymphocytes
* Chronic myeloid leukemia (CML) affects a type of white blood cell called granulocytes

Certain inheritable genetic syndromes also appear to raise risk for AML, although having one doesn’t mean you will develop leukemia. These include:

* Fanconi anemia
* Bloom syndrome
* Ataxia-telangiectasia
* Diamond-Blackfan anemia
* Shwachman-Diamond syndrome
* Li-Fraumeni syndrome
* Neurofibromatosis
* Kostmann syndrome

### Leukemia Prevention Tips

Because we don’t know exactly what causes leukemia, the National Cancer Institute doesn’t make specific suggestions on how to prevent it. However, it’s always a good idea to take steps to lower your overall risk of cancer through lifestyle modification. The following guidelines may be useful for leukemia prevention:

* Not using any tobacco products
* Not drinking alcohol
* Maintaining a body mass index below 25
* Being physically active every day
* Eating a diet rich in fruits and vegetables and low in processed meats

### Recommendations for Preventing Leukemia

While there’s no reliable way to prevent cholangiocarcinoma, the following bile duct cancer prevention recommendations may help you reduce your risk for developing the disease:

* Get vaccinated against hepatitis B and take steps to prevent infection with hepatitis C
* Limit alcohol use
* Don’t smoke
* Maintain a body mass index below 25
* Be physically active every day
* Eat a diet rich in fruits and vegetables and limit red and processed meat

**Diagnosis**

Doctors may find chronic leukemia in a routine blood test, before symptoms begin. If this happens, or if you have signs or symptoms that suggest leukemia, you may undergo the following diagnostic exams:

* **Physical exam.** Your doctor will look for physical signs of leukemia, such as pale skin from anemia, swelling of your lymph nodes, and enlargement of your liver and spleen.
* **Blood tests.** By looking at a sample of your blood, your doctor can determine if you have abnormal levels of red or white blood cells or platelets — which may suggest leukemia. A blood test may also show the presence of leukemia cells, though not all types of leukemia cause the leukemia cells to circulate in the blood. Sometimes the leukemia cells stay in the bone marrow.
* **Bone marrow test.** Your doctor may recommend a procedure to remove a sample of bone marrow from your hip bone. The bone marrow is removed using a long, thin needle. The sample is sent to a laboratory to look for leukemia cells. Specialized tests of your leukemia cells may reveal certain characteristics that are used to determine your treatment options.

**Treatment**

Treatment for your leukemia depends on many factors. Your doctor determines your leukemia treatment options based on your age and overall health, the type of leukemia you have, and whether it has spread to other parts of your body, including the central nervous system.

Common treatments used to fight leukemia include:

* **Chemotherapy.** Chemotherapy is the major form of treatment for leukemia. This drug treatment uses chemicals to kill leukemia cells.  
  Depending on the type of leukemia you have, you may receive a single drug or a combination of drugs. These drugs may come in a pill form, or they may be injected directly into a vein.
* **Targeted therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you.
* **Radiation therapy.** Radiation therapy uses X-rays or other high-energy beams to damage leukemia cells and stop their growth. During radiation therapy, you lie on a table while a large machine moves around you, directing the radiation to precise points on your body.  
  You may receive radiation in one specific area of your body where there is a collection of leukemia cells, or you may receive radiation over your whole body. Radiation therapy may be used to prepare for a bone marrow transplant.
* **Bone marrow transplant.** A bone marrow transplant, also called a stem cell transplant, helps reestablish healthy stem cells by replacing unhealthy bone marrow with leukemia-free stem cells that will regenerate healthy bone marrow.  
  Prior to a bone marrow transplant, you receive very high doses of chemotherapy or radiation therapy to destroy your leukemia-producing bone marrow. Then you receive an infusion of blood-forming stem cells that help rebuild your bone marrow.  
  You may receive stem cells from a donor or you may be able to use your own stem cells.
* **Immunotherapy.** Immunotherapy uses your immune system to fight cancer. Your body's disease-fighting immune system may not attack your cancer because the cancer cells produce proteins that help them hide from the immune system cells. Immunotherapy works by interfering with that process.
* **Engineering immune cells to fight leukemia.** A specialized treatment called chimeric antigen receptor (CAR)-T cell therapy takes your body's germ-fighting T cells, engineers them to fight cancer and infuses them back into your body. CAR-T cell therapy might be an option for certain types of leukemia.
* **Clinical trials.** Clinical trials are experiments to test new cancer treatments and new ways of using existing treatments. While clinical trials give you or your child a chance to try the latest cancer treatment, treatment benefits and risks may be uncertain. Discuss the benefits and risks of clinical trials with your doctor.

**Differential diagnosis**

* Acute myeloid leukemia
* Chronic myelomonocytic leukemia
* Chronic neutrophilic leukemia
* Thrombocythemia
* Leukemoid reactions from infections (chronic granulomatous [eg, tuberculosis])
* Tumor necrosis
* Acute Lymphoblastic Leukemia (ALL)
* Anemia
* Aplastic Anemia
* B-Cell Lymphoma
* Bone Marrow Failure
* Chronic Myelogenous Leukemia (CML)
* Lymphoblastic Lymphoma

## COMPLICATION

## Weakened immune system

Having a weakened immune system is a common complication of AML.

Even if your blood is restored to normal working order with treatment, many of the medicines that are used to treat AML can temporarily weaken your immune system.

This means you're more vulnerable to developing an infection, and any infection you develop could be more serious than usual.

Complications arising from infection are very common in people with AML. But if treated early, nearly all infections respond to appropriate treatment.

You may be advised to:

* take regular doses of antibiotics to prevent bacterial infections
* maintain good personal and dental hygiene
* avoid contact with anyone who's known to have an infection – even if it's a type of infection that you were previously immune to, such as chickenpox or measles
* check with your GP to make sure your vaccinations are up-to-date – you will not be able to have any vaccine that contains "live" viruses or bacteria, such as the shingles vaccine and MMR vaccine (against measles, mumps and rubella)

Report any possible symptoms of an infection to your treatment unit immediately as prompt treatment may be needed to prevent complications.

Symptoms of an infection can include:

* a sore throat
* a high temperature, and feeling hot or shivery (fever)
* flu-like symptoms, such as headaches, aching muscles and tiredness
* breathlessness or a cough
* pain when peeing

## Bleeding

If you have AML, you might bleed and bruise more easily because of the low levels of platelets (clot-forming cells) in your blood. Bleeding may also be excessive.

People with advanced AML are more vulnerable to excessive bleeding inside their body.

Serious bleeding can occur:

* inside the skull (intracranial haemorrhage) – causing symptoms such as a severe headache, stiff neck, vomiting and confusion
* inside the lungs (pulmonary haemorrhage) – causing symptoms such as coughing up blood, breathing difficulties and a bluish skin tone (cyanosis)
* inside the stomach (gastrointestinal haemorrhage) – causing symptoms such as vomiting blood and passing poos that are very dark or tar-like in colour

All these types of haemorrhage should be regarded as medical emergencies.

## Infertility

Most treatments used to treat AML can cause infertility. This is often temporary, but in some cases can be permanent.

People particularly at risk of permanent infertility are those who have received high doses of chemotherapy and radiotherapy in preparation for a bone marrow or stem cell transplant.

Your treatment team can talk to you about the risk of infertility in your specific circumstances and discuss any fertility options before you begin your treatment.

**EPIDEMIOLOGY**

Cancer Incidence Overview:

According to the World Health Organization, cancer claimed the lives of 41,000 Nigerians in 2018 out of

166,000 cases documented in the country. Nigeria was responsible for around 15.0% of Africa's estimated

681,000 new cancer cases in 2008. About 100,000 new cancer cases in Nigeria occur yearly

(Ferlay et al.,2010). The main reason for the significant increase in new cancer cases in Nigeria is; alcohol consumption,tobacco use, unhealthy diet, sedentary lifestyle, and polluted environments. Breast cancer, cervical cancer,prostate cancer,and blood cancer are Nigeria's standard and most prevalent cases

. Breast cancer is recognized as a significant cause of morbidity and mortality in Nigeria (Jedy-Agba et al., 2012).

Breast cancer remains the leading cause of death among African women(Tsoka-Gwegwenia et al., 2017).

A retrospective study conducted from January 2004 to December 2013 reported that 3,314 new cases of

Cancer was recorded in Lagos University Teaching Hospital (LUTH) during the study period. The mean age of cancer presentation is 48.52 ±16.44 years, and the male-to-female ratio was 1:3 (Sowunmi et al.,2018).Breast (38.1%), cervical (17.0%),and colorectal cancers (3.3%) are the most common ones recorded (Sowunmi et al., 2018). Another study found that 1436 (4.74%) cancer deaths out of 30287 deaths were recorded from death registers in the wards and mortuary over 14 years (2000–2013). The male-to-female

ratio was 1: 2.2. Overall, breast cancer was responsible for most deaths (Akinde et al., 2015).In other wealthy countries, the gender distribution is highly similar, but this ratio is exceptional (Wireduand Armah, 2006). Another 6-year (2014-2019) descriptive retrospective study conducted in the State tertiary health care center

in Delta State, Nigeria, reported that Cancer accounted for 668 (28.9%) of 2300 histologically diagnosed

cases, involving 461 females and 207 males with mean ages of 48.40 and 54.14 respectively. The combined sex mean age and age ranges were 50.17 and 1-98 years,respectively(Uchendu,2020).Themost

common cancers are breast (36.5%), colorectal (11.7%), prostate (8.1%), cervical (7.2%), soft tissue(6.0%), non-melanoma skin (5.2%), ovarian (4.0%),metastatic (4.0%), gastric (2.6%), thyroid (1.8%), and

salivary gland (1.4%) cancers (Uchendu, 2020).

A study from Ghana report Breast,cervical, hematolymphoid, cervical, prostate, liver, and colorectal malignancies as the most common type of

cancer (Wiredu & Armah, 2006).

Data from 2 population -based cancer registries(PBCRs )in Nigeria [Ibadan Population-Based Cancer Registry (IBCR) and the Abuja Population-Based Cancer Registry (ABCR)], covering two years 2009

–2010, a total of 3393 cancer cases were reported by the IBCR. Of these cases, 34.0% (1 155) were seen among males and 66% (2 238) in females. In Abuja, over the same period, 1128 invasive cancers

were reported. 33.6% (389) of these cases were males ,and 66.4%(768)infemales. The Mean age of diagnosis of all cancers in men for Ibadan and Abuja was 51.1 and 49.9 years, respectively. For women, the mean age of all cancers diagnosed in Ibadan and Abuja was 49.1 and 45.4, respectively (Jedy-Agba et al.,2012). Breast and cervical cancer were the most typical cancers among women, and prostate cancer was the most common among men (Jedy-Agba et al.,2012).Another study conducted between Nigeria and neighboring countries (Benin, Cameroun, Chad,Niger) found that the most common male cancer in Nigeria and border countries are Prostate cancer, seconded by Liver. In this study, also we found Breast cancer to be the most common in females, followed by

Cervical Cancer. Larynx and Kaposi sarcoma are the least common cancer for both males and females in the

population (Baba et al., 2018).A study reviewed clinical records of confirmed breast cancer patients between January 2011 and December 2015 at the Ekiti State University Teaching Hospital,Nigeria, found that eighty two breast cancer patients were seen. Their ages ranged from 26-95 years (mean48.9±14.9years,median 47.5 years).Eighty-one(98.8%) were females, and the majority (65.4%) were premenopausal (Olaogun et al., 2020). Between 2012 and 2014, the PBCRs reported

4,336 incident cancer cases, including 1,627(37.5%)malesand2,709(62.5%) females. Infections were linked to 1,030(23.8%) of these malignancies, while 951 (22.0%)were caused by infections. Cervical and liver cancers,

non-lymphoma,and Hodgkin's Were The Most Common Infection-related cancers HPV,EBV

November-December, 2022 hepatitis B and C, HIV, and HHV8 were the most common infectious agents linked to cancer in this population (Odutola et al.,2016).According to aten-year assessment of Port Harcourt cancer registry data,males accounted for 1,191 (44.4%) of the 2,682 malignancies recorded, while females accounted for 1,491 (55.6%). The average age of the participants was 51.9 years. Breast cancer (29.0%), prostate cancer(25.2%),cervix cancer (6.6%),colorectal cancer (5.4%), and leukemia (4.3%) were the five most prevalent cancer locations (Christopher et al. 2019).Patients of African ancestry have the poorest outcome

and the shortest survival rates from cancer globally. This could be attributed to many variables

,including racial, biological, socioeconomic,and socio-cultural factors, which may be responsible for this

significant health problem (Bahnassy et al., 2020).

MostCommon Cancer Type in Nigeria:

•Breast cancer

•Prostate cancer

•Cervix Uteri

•Colorectal cancer

•Non-Hodgkin lymphoma

•Liver cancer

•Leukemia

•Ovarian Cancer

**RECENT GUIDELINE FROM NCI**

Leukaemia leads to the overproduction of abnormal white blood cells. These abnormal cells usually can’t carry out the normal functions of white blood cells. They crowd the bone marrow and spill into the blood and may then spread into organs such as the lymph nodes, spleen, liver, the brain and spinal cord, lungs, kidneys and testicles, where they can keep other cells in the body from doing their jobs.

Symptoms of leukaemia are notoriously vague and non-specific. This is partly responsible for the late detection and high mortality in Nigeria. It is therefore important for everyone to be aware of these symptoms and to report promptly to the hospital for evaluation. In leukaemia symptoms are more commonly caused by lack of normal blood cells than by the presence of abnormal white cells. As the bone marrow becomes full of leukaemia cells, it is unable to produce the large numbers of normal blood cells, which the body needs.

This leads to: Anaemia – due to lack of red blood cells, causing paleness, weakness, shortness of breath and tiredness; Recurrent infections – due to lack of normal white blood cells; Bleeding and bruising – due to lack of platelets. Other symptoms include Fever, Malaise (feeling unwell) and excessive sweating. In children, there may be pain in bones or joints. There may also be swelling of the belly due to enlargement of the liver (hepatomegaly) or the spleen (an organ of the immune system found just under the ribs on the left hand side) (splenomegaly).

Leukaemia results from damage to the DNA. The cause of this damage is unknown in most cases of leukaemia. However, there are certain ‘risk factors’ which increase the chance of developing leukaemia. These include: Gender – leukaemias are generally more common in males; Genetics – there is a slightly higher chance of development of some forms of leukaemia in close relatives of patients. Smoking; Chemotherapy or other medicines that weaken the immune system; and Certain genetic disorders like Down’s syndrome could also predispose an individual to the disease. Intense exposure to radiation, including radiotherapy for another condition can also lead to leukaemia.

For instance, many of the survivors of the atomic bomb used in World War II developed leukaemia due to the fall-out of radiation. However, no leukaemia has been linked to radiation from x-rays and CT scans.

Another important risk factor for leukaemia is exposure to certain chemicals such as benzene. It is instructive to note that according to the report of the United Nations Environment Programme (UNEP) released in August 2011 on its Environmental Assessment of Ogoniland, drinking water in some areas is contaminated with benzene, at levels 900 times above the WHO guideline.

In addition, benzene was detected in air samples at higher levels than stipulated by WHO. So one could imagine the number of people in these communities who are dying silently from leukaemia and other cancers related to environmental pollution. Most of these cases are never diagnosed due to absence of basic infrastructure for cancer care.

The current statistics of five (5) Nigerians dying of leukaemia every day is thus probably an underestimation. Sadly, the effect of this pollution will out-last the present generation.

The recent move by the Government of Nigeria to fast track the recommendations of UNEP, which had been ignored for four years is commendable. However, government must sustain the political will to ensure that the recommendations are followed through and not abandoned half way. All the other stakeholders, including the oil companies and the members of the affected communities should also play their roles in ensuring a comprehensive and sustained clean-up of these areas whilst preventing future contaminations, in Ogoniland and other oil-producing areas.

The gold standard for the treatment of some forms of leukaemia is stem cell transplant. A stem cell transplant is a procedure that replaces unhealthy stem cells with healthy ones. Stem cell transplant offers a potential cure for blood cancers such as leukemia, lymphoma, and other life-threatening diseases including aplastic anaemia and sickle cell anaemia.

A shining example of how this procedure can give a new lease of life to leukaemia patients is the Nigerian-American Oluwaseun Adebiyi. Thirty- two year old Seun is a graduate of the Yale Law School, a former corporate attorney at Goldman Sachs, and a trained pilot. Seun survived leukaemia (diagnosed a week before his 26th birthday), because he had access to stem cell transplant at the Memorial Sloan-Kettering Cancer Centre, in Manhattan, USA. That experience transformed and redirected his life.

Today he is a Project Manager of the American Cancer Society as well as the Founder/CEO of the Bone Marrow Registry in Nigeria (“BMRN”), Enugu. The BMRN is a not-for-profit organization established in 2012 to connect stem cell donors with patients who need stem cell transplant. If Seun had been in Nigeria rather than in the USA, he would most likely not be with us today.

In 2011, the University of Benin Teaching Hospital (UBTH) successfully pioneered stem cell transplantation in Nigeria. Unfortunately, the UBTH facility has fallen to desuetude, mainly because at five million naira per patient the cost of the procedure is beyond the reach of most Nigerians. Since inception four (4) years ago, only three (3) cases of Sickle Cell Anaemia have benefited from this procedure that is now available locally. Meanwhile, Nigeria has one of the highest incidences of sickle cell anemia in the world! No case of leukaemia has been treated. What a waste of scarce resources! Nigeria should as a matter of urgency provide subsidy to bring this life-saving treatment within the reach of the common man.

The sad situation at UBTH also underscores the importance of focusing first and foremost on prevention which is cheaper and surer. Even if the best of treatment were available, it would be useless if the illness is not diagnosed. It is important to note that the results of a simple blood count could help to diagnose leukaemia; yet most Nigerians get picked up late, leading to the high mortality. An excellent starting point in the effort to ensure access to optimal, accessible and affordable preventive healthcare is through the use of the Mobile Cancer Centres (MCC), as being championed by Committee Encouraging Corporate Philanthropy (CECP-Nigeria) for the BIG War Against Cancer.

CECP’s operational partner for the BIG War Against Cancer is the National Cancer Prevention Programme (NCPP), a non-governmental initiative founded in 2007. Over 100,000 Nigerians have been directly screened and treated so far, and through the awareness created, the NCPP is helping to protect millions of Nigerians from cancer. This monumental effort has contributed immensely to the reduction of cervical cancer deaths in Nigeria from 26 daily in 2008 to 22 daily in 2012 (WHO data). The MCC will facilitate the process of scaling up this effort.

An MCC is much more than a Mobile Mammogram. Rather, it is a clinic on wheels, in which screening, follow-up and treatment (including surgeries), can take place. It includes facilities for mammography, sonology, colonoscopy, colposcopy and cryotherapy, as well as a surgical theatre. It is also equipped with facilities for screening against most common diseases, including the Ten Major Cancer-related killer diseases (Diabetes, Renal Disease, Obesity, Malaria, Schistosomiasis, Helicobacter pylori, Hepatitis, HIV/AIDS, Human Papillomavirus (HPV) and Hypertension). Thus the MCC would tackle the double burden of disease, i.e. Communicable & Non-Communicable.

The MCC is perhaps the single most important means of raising the life expectancy of Nigeria which is currently the 12th lowest globally. Cancer and these ten disease conditions are the main culprits responsible for this low life expectancy. A single MCC in a state of Nigeria could make a huge positive difference. That state would be divided into smaller units such that every community would be reached by the Mobile Cancer Centre at least once a year.

The cost of one MCC is $600,000 only (about N120, 000, 000 at the current exchange rate) and its operational cost for one year (including cost of personnel, supplies and maintenance), is $685,000.

REFERENCES

<https://www.nhs.uk/conditions/acute-myeloid-leukaemia/complications/>

[Leukemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/leukemia/diagnosis-treatment/drc-20374378)

<https://www.researchgate.net/publication/366325652_The_Cancer_is_Silently_Killing_Nigerians_An_Explanatory_Study>

**ACUTE LYMPHOCYTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute lymphocytic leukemia (ALL) is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made.

The word "acute" in acute lymphocytic leukemia comes from the fact that the disease progresses rapidly and creates immature blood cells, rather than mature ones. The word "lymphocytic" in acute lymphocytic leukemia refers to the white blood cells called lymphocytes, which ALL affects. Acute lymphocytic leukemia is also known as acute lymphoblastic leukemia.

Acute lymphocytic leukemia is the most common type of cancer in children, and treatments result in a good chance for a cure. Acute lymphocytic leukemia can also occur in adults, though the chance of a cure is greatly reduced.

**Causes**

Acute lymphocytic leukemia occurs when a bone marrow cell develops changes (mutations) in its genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In acute lymphocytic leukemia, the mutations tell the bone marrow cell to continue growing and dividing.

When this happens, blood cell production becomes out of control. The bone marrow produces immature cells that develop into leukaemia white blood cells called lymphoblasts. These abnormal cells are unable to function properly, and they can build up and crowd out healthy cells.

It's not clear what causes the DNA mutations that can lead to acute lymphocytic leukemia.

**Risk factors**

Factors that may increase the risk of acute lymphocytic leukemia include:

* **Previous cancer treatment.** Children and adults who've had certain types of chemotherapy and radiation therapy for other kinds of cancer may have an increased risk of developing acute lymphocytic leukemia.
* **Exposure to radiation.** People exposed to very high levels of radiation, such as survivors of a nuclear reactor accident, have an increased risk of developing acute lymphocytic leukemia.
* **Genetic disorders.** Certain genetic disorders, such as Down syndrome, are associated with an increased risk of acute lymphocytic leukemia.

**Symptoms**

Signs and symptoms of acute lymphocytic leukemia may include:

* Bleeding from the gums
* Bone pain
* Fever
* Frequent infections
* Frequent or severe nosebleeds
* Lumps caused by swollen lymph nodes in and around the neck, armpits, abdomen or groin
* Pale skin
* Shortness of breath
* Weakness, fatigue or a general decrease in energy

**DIAGNOSIS AND TEST**

Tests and procedures used to diagnose acute lymphocytic leukemia include:

* **Blood tests.** Blood tests may reveal too many or too few white blood cells, not enough red blood cells, and not enough platelets. A blood test may also show the presence of blast cells — immature cells normally found in the bone marrow.
* **Bone marrow test.** During bone marrow aspiration and biopsy, a needle is used to remove a sample of bone marrow from the hipbone or breastbone. The sample is sent to a lab for testing to look for leukemia cells.  
  Doctors in the lab will classify blood cells into specific types based on their size, shape, and other genetic or molecular features. They also look for certain changes in the cancer cells and determine whether the leukemia cells began from B lymphocytes or T lymphocytes. This information helps your doctor develop a treatment plan.
* **Imaging tests.** Imaging tests such as an X-ray, a computerized tomography (CT) scan or an ultrasound scan may help determine whether cancer has spread to the brain and spinal cord or other parts of the body.
* **Spinal fluid test.** A lumbar puncture test, also called a spinal tap, may be used to collect a sample of spinal fluid — the fluid that surrounds the brain and spinal cord. The sample is tested to see whether cancer cells have spread to the spinal fluid.

### Determining your prognosis

Your doctor uses information gathered from these tests and procedures to determine your prognosis and decide on your treatment options. Other types of cancer use numerical stages to indicate how far the cancer has spread, but there are no stages of acute lymphocytic leukemia.

Instead, the seriousness of your condition is determined by:

* The type of lymphocytes involved — B cells or T cells
* The specific genetic changes present in your leukemia cells
* Your age
* Results from lab tests, such as the number of white blood cells detected in a blood sample

**Treatment**

In general, treatment for acute lymphocytic leukemia falls into separate phases:

* **Induction therapy.** The purpose of the first phase of treatment is to kill most of the leukemia cells in the blood and bone marrow and to restore normal blood cell production.
* **Consolidation therapy.** Also called post-remission therapy, this phase of treatment is aimed at destroying any remaining leukemia in the body.
* **Maintenance therapy.** The third phase of treatment prevents leukemia cells from regrowing. The treatments used in this stage are usually given at much lower doses over a long period of time, often years.
* **Preventive treatment to the spinal cord.** During each phase of therapy, people with acute lymphocytic leukemia may receive additional treatment to kill leukemia cells located in the central nervous system. In this type of treatment, chemotherapy drugs are often injected directly into the fluid that covers the spinal cord.

Depending on your situation, the phases of treatment for acute lymphocytic leukemia can span two to three years.

Treatments may include:

* **Chemotherapy.** Chemotherapy, which uses drugs to kill cancer cells, is typically used as an induction therapy for children and adults with acute lymphocytic leukemia. Chemotherapy drugs can also be used in the consolidation and maintenance phases.
* **Targeted therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you. Targeted therapy can be used alone or in combination with chemotherapy for induction therapy, consolidation therapy or maintenance therapy.
* **Radiation therapy.** Radiation therapy uses high-powered beams, such as X-rays or protons, to kill cancer cells. If the cancer cells have spread to the central nervous system, your doctor may recommend radiation therapy.
* **Bone marrow transplant.** A bone marrow transplant, also known as a stem cell transplant, may be used as consolidation therapy or for treating relapse if it occurs. This procedure allows someone with leukemia to reestablish healthy bone marrow by replacing leukemic bone marrow with leukemia-free marrow from a healthy person.  
  A bone marrow transplant begins with high doses of chemotherapy or radiation to destroy any leukemia-producing bone marrow. The marrow is then replaced by bone marrow from a compatible donor (allogeneic transplant).
* **Engineering immune cells to fight leukemia.** A specialized treatment called chimeric antigen receptor (CAR)-T cell therapy takes your body's germ-fighting T cells, engineers them to fight cancer and infuses them back into your body.  
  CAR-T cell therapy might be an option for children and young adults. It might be used for consolidation therapy or for treating relapse.
* **Clinical trials.** Clinical trials are experiments to test new cancer treatments and new ways of using existing treatments. While clinical trials give you or your child a chance to try the latest cancer treatment, the benefits and risks of the treatment may be uncertain. Discuss the benefits and risks of clinical trials with your doctor.

### Treatment for older adults

Older adults, such as those older than 65, tend to experience more complications from treatments. And older adults generally have a worse prognosis than children who are treated for acute lymphocytic leukemia.

Discuss your options with your doctor. Based on your overall health and your goals and preferences, you may decide to undergo treatment for your leukemia.

Some people may choose to forgo treatment for the cancer, instead focusing on treatments that improve their symptoms and help them make the most of the time they have remaining.

**Alternative medicine**

No alternative treatments have been proved to cure acute lymphocytic leukemia. But some alternative therapies may help ease the side effects of cancer treatment and make you or your child more comfortable. Discuss your options with your doctor, as some alternative treatments could interfere with cancer treatments, such as chemotherapy.

Alternative treatments that may ease symptoms include:

* Acupuncture
* Exercise
* Massage
* Meditation
* Relaxation activities, including yoga and tai chi

### When to see a doctor

Make an appointment with your doctor or your child's doctor if you notice any persistent signs and symptoms that concern you.

Many signs and symptoms of acute lymphocytic leukemia mimic those of the flu. However, flu signs and symptoms eventually improve. If signs and symptoms don't improve as expected, make an appointment with your doctor.

**DIFFERENTIAL DIAGNOSIS**

* B cell lymphoma
* Acute myeloid leukemia
* Non-Hodgkin lymphoma

**EPIDEMIOLOGY**

It is diagnosed in about 4000 people in the United States each year, with the majority being under the age of 18. It is the most common malignancy of childhood. The peak age of diagnosis is between two and ten years of age.

Acute Lymphocytic Leukemia is more common in children with Trisomy 21 (Down syndrome), neurofibromatosis type 1, Bloom syndrome, and ataxia telangiectasia. All are common in children between two and three years of age. Prognosis is diminished in children when diagnosed in infants less than one year of age and in adults. It is more favorable in children. The association of the MLL gene in children at the 11q23 chromosome is associated with poor prognosis. Acute lymphocytic leukemia is a disease with low incidence overall in population studies. The incidence of acute lymphocytic leukemia is about 3.3 cases per 100,000 children. Survival rates for ALL have improved dramatically since the 1980s, with a current five-year overall survival rate estimated at greater than 85 percent.

REFERENCES

[Acute Lymphocytic Leukemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK459149/#article-17157.s10)

[Acute lymphocytic leukemia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/symptoms-causes/syc-20369077)

[Acute lymphocytic leukemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/diagnosis-treatment/drc-20369083)

**ACUTE MYELOGENOUS LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute myelogenous leukemia, also called AML, is a cancer of the blood and bone marrow. Bone marrow is the soft matter inside bones where blood cells are made.

The word "acute" in acute myelogenous leukemia means the disease tends to get worse quickly. It's called myelogenous (my-uh-LOHJ-uh-nus) leukemia because it affects cells called the myeloid cells. These typically develop into mature blood cells, including red blood cells, white blood cells and platelets.

AML is the most common type of acute leukemia in adults. The other type is acute lymphoblastic leukemia, also called ALL. Although AML can be diagnosed at any age, it is less common before age 45. AML also is called acute myeloid leukemia, acute myeloblastic leukemia, acute granulocytic leukemia and acute nonlymphocytic leukemia.

Unlike other cancers, there are no numbered stages of acute myelogenous leukemia.

**Causes**

It's often not clear what causes acute myelogenous leukemia.

Healthcare professionals know that it starts when something causes changes to the DNA inside cells in the bone marrow. The bone marrow is the spongy material inside bones. It's where blood cells are made.

The changes that lead to acute myelogenous leukemia are thought to happen in cells called myeloid cells. Myeloid cells are bone marrow cells that can turn into the blood cells that circulate through the body. Healthy myeloid cells can become:

* Red blood cells, which carry oxygen to the body.
* Platelets, which help stop bleeding.
* White blood cells, which help fight infections.

Every cell in the body contains DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. But when the DNA changes happen in the myeloid cells, the changes give different instructions. The myeloid cells start to make a lot of extra cells, and they don't stop.

The DNA changes cause the myeloid cells to make a lot of immature white blood cells, called myeloblasts. The myeloblasts don't work right. They can build up in the bone marrow. They can crowd out healthy blood cells. Without enough healthy blood cells, there might be low oxygen levels in the blood, easy bruising and bleeding, and frequent infections.

**Risk factors**

Factors that may increase the risk of acute myelogenous leukemia, also called AML, include:

* **Older age.** Acute myelogenous leukemia is most common in adults age 65 and older.
* **Prior cancer treatment.** People who've had certain types of chemotherapy and radiation therapy may have a greater risk of AML.
* **Radiation exposure.** People exposed to very high levels of radiation, such as a nuclear reactor accident, have an increased risk of developing AML.
* **Dangerous chemical exposure.** Certain chemicals, such as benzene, are linked to a greater risk of AML.
* **Smoking cigarettes.** AML is linked to cigarette smoke, which contains benzene and other known cancer-causing chemicals.
* **Other blood disorders.** People who've had another blood disorder, such as myelodysplasia, myelofibrosis, polycythemia vera or thrombocythemia, are at greater risk of AML.
* **Genetic disorders.** Certain genetic disorders, such as Down syndrome, are associated with an increased risk of AML.
* **Family history.** People with a close blood relative, such as a sibling, parent or grandparent with a blood or bone marrow disorder are at higher risk for AML.

Many people with AML have no known risk factors, and many people who have risk factors never develop cancer.

**Symptoms**

Symptoms of acute myelogenous leukemia may include:

* Fever.
* Pain. Common places for pain include the bones, back and stomach.
* Feeling very tired.
* Paleness or change in skin color.
* Frequent infections.
* Easy bruising.
* Bleeding with no clear cause, such as in the nose or gums.
* Shortness of breath.

**DIAGNOSIS AND TEST**

Acute myeloid leukemia diagnosis often begins with an exam that checks for bruising, bleeding in the mouth or gums, infection, and swollen lymph nodes. Other tests include blood and lab tests, bone marrow biopsy, lumbar puncture, and imaging.

Tests and exams to diagnose acute myelogenous leukemia, also called AML, include:

### Blood tests

Blood tests for acute myelogenous leukemia might include a test to count the number of blood cells in a sample of blood. This test is called a complete blood count. The results may show too many or too few white blood cells. Often the test finds that there are not enough red blood cells and not enough platelets. Another blood test looks for immature white blood cells called myeloblasts in the blood. These cells typically aren't found in the blood. But they can occur in the blood of people with AML.

### Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. In bone marrow aspiration, a needle is used to draw a sample of the bone marrow fluid. In a bone marrow biopsy, a needle is used to collect a small amount of solid tissue. The samples are typically taken from the hip bone. The samples go to a lab for testing.

In the lab, tests can look for DNA changes in the bone marrow cells. Which DNA changes are present in your bone marrow cells are an important part of diagnosing AML. The results can help your healthcare team create a treatment plan.

### Lumbar puncture

Sometimes, a lumbar puncture may be needed if there's concern that the leukemia has spread to the brain and spinal cord. A lumbar puncture also is called a spinal tap. It removes a sample of the fluid that surrounds the brain and spinal cord. A small needle is inserted into the lower back to remove a fluid sample. The sample is sent to a lab.

### Imaging tests

Imaging tests make pictures of the body. For AML, imaging tests might make pictures of the brain, if there's concern that the leukemia cells have spread there. Imaging might include CT or MRI. If there's concern that the leukemia might have spread to another part of the body, imaging might be done with a positron emission tomography scan, also called a PET scan.

### Your AML subtype

If you're diagnosed with AML, you may need further lab tests to determine your AML subtype. These tests include examining your blood and bone marrow for genetic changes and other signs that indicate specific AML subtypes. Currently, there are 15 different subtypes. Your AML subtype helps your healthcare professional determine the best treatment for you.

**Treatment**

Many types of treatment exist for acute myelogenous leukemia, also called AML. Treatment depends on several factors, including the subtype of the disease, your age, your overall health, your prognosis and your preferences.

Treatment usually has two phases:

* **Remission induction therapy.** This first phase aims to kill the leukemia cells in your blood and bone marrow. But it doesn't usually destroy all the leukemia cells. You will need further treatment to keep the disease from coming back.
* **Consolidation therapy.** This phase also is called post-remission therapy or maintenance therapy. It aims to kill the remaining leukemia cells. Consolidation therapy is crucial to helping lower the risk of relapse.

Treatments include:

**Chemotherapy.** Chemotherapy treats cancer with strong medicines. Most chemotherapy medicines are given through a vein. Some come in pill form. Chemotherapy is the main type of remission induction therapy. It also may be used for consolidation therapy.

People with AML usually stay in the hospital during chemotherapy treatments because the medicines kill many healthy blood cells while destroying leukemia cells. If the first chemotherapy cycle doesn't cause remission, it can be repeated.

Side effects of chemotherapy depend on the medicines you're given. Common side effects are nausea and hair loss. Serious, long-term complications may include heart disease, lung damage, fertility problems and other cancers.

**Targeted therapy.** Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you. Targeted therapy may be used alone or in combination with chemotherapy during induction therapy.

**Bone marrow transplant.** A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. A bone marrow stem cell transplant may be used for both remission induction and consolidation therapy.

Before a bone marrow transplant, you receive very high doses of chemotherapy or radiation therapy to destroy your leukemia-producing bone marrow. Then you receive infusions of stem cells from a compatible donor. This is called an allogeneic transplant.

There is an increased risk of infection after a transplant.

**Alternative medicine**

No alternative treatments have been found to treat acute myelogenous leukemia. But integrative medicine may help you cope with the stress of a cancer diagnosis and side effects of your treatment.

Alternative treatments that may help relieve symptoms include:

* Acupuncture.
* Exercise.
* Massage.
* Meditation.
* Relaxation activities, such as yoga.
* Art and music therapy.

### When to see a doctor

Make an appointment with your healthcare professional if you have ongoing symptoms that worry you. Acute myelogenous leukemia symptoms are like those of many more-common conditions, such as infections. The healthcare professional may check for those causes first.

## Outlook / Prognosis

Currently, allogeneic stem cell transplantation is the only way to cure acute myeloid leukemia. Depending on your situation, your provider may recommend stem cell transplantation as your first AML treatment or if you have AML that comes back within 12 months. Unfortunately, not everyone may be a candidate for stem cell transplantation.

#### What is the prognosis for AML?

There are two sides of the coin in acute myeloid leukemia prognosis. One side is complete remission. The other is recurrence, when AML comes back:

* Overall, an estimated 50% to 80% of people with acute myeloid leukemia achieve complete remission after treatment. Complete remission happens more often in children and people under age 60. Remission may last for months or years.
* About 50% of people who achieve complete remission develop recurrent AML. When that happens, providers may recommend additional chemotherapy or stem cell transplantation. They may suggest participation in a clinical trial.

If you or your child has AML, ask your provider to explain what you can expect.

#### What is the survival rate of acute myeloid leukemia?

Acute myeloid leukemia is a complicated illness. There are several AML subtypes, which makes it difficult to be specific about survival rates.

For example, the five-year survival rate for children under age 15 is 67%. But some research suggests that the five-year survival rate increases to more than 80% in children who have the APL subtype. And age makes a difference. In general, 30% of adults with acute myeloid leukemia are alive five years after diagnosis. Remember, AML typically affects people age 60 and older who may have other health issues.

It’s important to remember that survival rates reflect the experiences of large groups of people with AML. In this case, survival rate data includes survival rates from 2012 to 2018, and there are some new and more effective treatments for AML.

Many things affect how long you’ll live with acute myeloid leukemia. That means your healthcare providers, the people who know your medical history and your overall health, are your best resources for information.

## Prevention

No, you can’t prevent acute myeloid leukemia. Experts know that genetic mutations cause acute myeloid leukemia but they don’t know what triggers them. They do know about risk factors that may cause AML. Risk factors you can modify include:

* Smoking, including exposure to second-hand smoke. If you smoke, try to quit. If you live or work around someone who smokes, try to limit how much time you spend with them when they’re smoking.
* Long-term exposure to certain carcinogenic chemicals, particularly benzene and formaldehyde. If you work around these carcinogens, be sure you follow all safety precautions, such as wearing protective clothing.

## Living With

It’s not easy to live with cancer that may come back. Getting involved with cancer survivorship programs is one way to take care of yourself. You may not be able to keep acute myeloid leukemia from coming back. But you can take steps to be as healthy as possible, no matter what. Here are some suggestions:

* Treatments for acute myeloid leukemia may affect your diet. You need to eat well to stay strong. If you’re having trouble eating, ask to speak to a nutritionist.
* AML treatment side effects can be hard to manage. If you need to, talk to your provider about palliative care.
* Cancer is stressful. You may be able to manage stress with exercise. But check with your provider before starting a new or aggressive exercise program.
* Cancer can be lonely. AML is a rare disease. You may feel anxious about discussing your situation. In that case, consider joining a support group.
* Acute myeloid leukemia can be exhausting. Treatment may sap your energy. Try to remember to get as much sleep as you need.

**DIFFERENTIAL DIAGNOSIS**

Other diseases with presentations similar to AML include Acute lymphoblastic leukemia, anemia, aplastic anemia, B-cell lymphoma, bone marrow failure, chronic myelogenous leukemia, lymphoblastic lymphoma, MDS, myelophthisic anemia, and primary myelofibrosis.

**EPIDEMIOLOGY**

The annual incidence of new cases in both men and women is approximately 4.3 per 100,000 population, totaling over 20,000 cases per year in the United States alone. The median age at the time of diagnosis is about 68, with a higher prevalence observed among non-Hispanic Whites. Furthermore, males exhibit a higher incidence compared to females, with a ratio of 5:3.

## 

## Updates on Treatments in Newly Diagnosed AML

## The classical paradigm to achieve cure in AML is first to induce CR thereby reducing the leukemia burden by several orders of magnitude, followed by post‐remission therapy in the form of chemotherapy and/or alloSCT. The choice of the most appropriate induction and post‐remission therapy is based on multiple parameters, including patient comorbidities, past medical history including prior myeloid disease and/or cytotoxic chemotherapy exposure, AML cytogenetic and molecular risk profile, possibly post‐therapy MRD status, as well as donor availability and patient goals of care. Historically, the first step for deciding on initial treatment is based on patients 'fitness for intensive therapy, with intensive chemotherapy induction being the default for those who are being deemed fit for a highly myelosuppressive/gut‐toxic approach. It is perhaps easier to delineate who should not receive intensive chemotherapy than who should definitely be subject to a long hospitalization with a significant risk of treatment‐related mortality. At this time, age over 75 is thought to be a relative contraindication to intensive chemotherapy, especially based on the known availability of effective less intensive chemotherapy. Other than age, the FDA has adopted a set of stringent criteria (poor hepatic, renal, cardiac, and pulmonary function) to definitively consider a patient unfit for intensive chemotherapy. The criteria are commonly incorporated into eligibility criteria and were validated in a large cohort of patients for predicting shorter‐term mortality after intensive chemotherapy treatment in AML. However, with multiple therapeutics emerging in recent years, the paradigm has shifted toward “who would benefit from intensive chemotherapy” rather than who is deemed fit. For instance, even a ‘fit’ patient (of any age) with adverse risk biology might not be “appropriate” for intensive chemotherapy due the likelihood of poor outcomes. The dilemma is most prominent in patients aged 60–75 years, which represents the largest age group in AML, many of whom can potentially be treated with either intensive or less‐intensive therapies in the upfront setting. We will elaborate on the various therapeutic possibilities and present our approach, including an updated suggested therapeutic algorithm for patients in this age group.

### 6.2. Updates on Intensive Therapy for Newly Diagnosed Patients

### The backbone of intensive chemotherapy remains an anthracycline‐ and cytarabine‐based approach, most commonly as the “7 + 3” regimen using daunorubicin at a dose of 60–90 mg/m2 for 3 days and cytarabine at a dose of 100–200 mg/m2 for 7 days. However, other induction regimens in use include CLAG‐M, G‐CLAM, IA, FLAG‐IDA, and lomustine‐IA. Whether any of these are ‘better’ than 3 + 7 alone is unclear, though the addition of either lomustine, a nucleoside analog, or treatment with FLAG‐IDA have each been suggested to be superior to 3 + 7 in prospective randomized trials; however, the latter was deemed too toxic for general use. Moreover, several drugs were recently approved (in combination with chemotherapy) for patients with newly diagnosed (ND) AML who are fit for intensive chemotherapy. Regarding the dose of daunorubicin, in two large‐randomized trials, 90 versus 45 mg/m2 improved survival among younger and older patients, as well as in patients with specific mutations (*NPM1*, *FLT3*, and *DNMT3A*). However, there was no benefit in term of survival among 1206 patients with AML when 90 mg/m2 was compared to 60 mg/m2 (although all patients received a second course of daunorubicin 50 mg/m2, which could potentially reduce the beneficial effects of 90 vs. 60 mg/m2). The two‐step randomized DAUNODOUBLE trial evaluated daunorubicin intensity and the additive value of second induction in 864 patients aged 18–65 years with ND AML treated with intensive chemotherapy. In the first randomization, there was no difference in response or survival in patients treated with 60 mg/m2 compared with 90 mg/m2 (composite CR rates: 90% vs. 89%, *p* = 0.691; 3‐year OS 65% vs. 58%, *p* = 0.242, respectively). In subgroup analyses, comparable outcomes were seen across patients with *NPM1*, *FLT3‐*ITD, and all ELN 2017 risk groups. In the second randomization, there was no benefit of a second induction among the 389 who achieved a good early response (defined as < 5% blasts in the day‐14 bone marrow evaluation): composite CR rates 87% versus 85%; 3‐year OS 76% versus 75% with one vs. two inductions, respectively.

REFERENCES

[Acute Myeloid Leukemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK507875/#article-25443.s9)

[Acute Myeloid Leukemia (AML): Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/6212-acute-myeloid-leukemia-aml#outlook-prognosis)

[Acute myelogenous leukemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/acute-myelogenous-leukemia/diagnosis-treatment/drc-20369115)

[Acute myelogenous leukemia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/acute-myelogenous-leukemia/symptoms-causes/syc-20369109)

### 

### 

### Acute promyelocytic leukemia (APL)

**DEFINITION AND DESCRIPTION**

Acute promyelocytic leukemia (APL) is a rare blood cancer. It’s a form of acute myeloid leukemia that happens when a genetic mutation (change) creates abnormal white blood cells that multiply uncontrollably in your bone marrow. Healthcare providers may call this condition APL leukemia or M3-leukemia.

APL is a serious condition with life-threatening symptoms, including excessive bleeding, which come on suddenly and quickly get worse. Thanks to treatment that’s an innovative combination of chemotherapy and non-chemotherapy drugs, healthcare providers can treat and often cure acute promyelocytic leukemia.

## Symptoms and Causes

Acute promyelocytic leukemia (APL) symptoms develop when your bone marrow can’t make normal numbers of red blood cells, white blood cells and platelets. If you have low blood cell levels (pancytopenia), you may develop serious symptoms, including anemia, bleeding issues (hemorrhage) and infections.

Other APL symptoms are:

* Fatigue from anemia, or low red blood cells.
* Frequent infections because you have low levels of infection-fighting white blood cells.
* Unintentional weight loss because your metabolism speeds up and you burn energy from food.

#### Bleeding symptoms

In acute promyelocytic leukemia, you don’t have enough platelets or blood clotting factors. Platelets slow or stop bleeding. Blood clotting factors help make clots in your blood. APL bleeding symptoms include:

* Bleeding from any site, including bleeding gums, nosebleeds or heavy menstrual bleeding.
* Bruising from blood pooling under your skin.
* Difficulty moving your arms and legs, headaches or vision issues from bleeding into your brain (intracranial hemorrhage).
* Poop that looks black or has red streaks of blood. This happens if you have bleeding in your gut (gastrointestinal bleeding).

### Causes of acute promyelocytic leukemia

This condition happens when two genes that drive blood cell development fuse to create the abnormal gene *PML-RARa*. You don’t inherit this genetic mutation (change). It happens randomly during your lifetime. Experts don’t know what triggers the change.

The mutation keeps white blood cells from developing as they should. The immature white blood cells (promyelocytes) multiply uncontrollably, crowding out healthy blood cells and platelets.

### complications of APL

APL can be life-threatening, causing severe bleeding that quickly gets worse. Contact a healthcare provider or go to the emergency department if you have bleeding that you can’t control, like bleeding from a cut or injury or there’s lots of blood in the toilet after you poop or pee or bleeding gums.

## Diagnosis and Tests

Healthcare providers typically order the following tests to diagnose this condition:

* Complete blood count (CBC): APL creates abnormal white blood cells. CBC tests show the number of blood cells and platelets in a blood sample.
* Peripheral blood smear: Providers may see high levels of granules or Auer rods inside promyelocytes, a specific type of white blood cell.
* Bone marrow biopsy: Providers order these to get samples of your bone marrow cells for analysis.
* Flow cytometry: In this test, pathologists examine the surface of abnormal cells, checking for specific protein patterns that confirm APL.
* Polymerase chain reaction (PCR) test: This test checks for the abnormal gene that causes APL.
* Cytogenetics: Pathologists will examine abnormal cells for specific changes in chromosomes. Finding those changes is how providers confirm an APL diagnosis.

Healthcare providers use white blood cell counts to classify cases as being low- or high-risk APL. People with high-risk acute promyelocytic leukemia are more likely to experience relapse (recurrent cancer).

## Management and Treatment

APL treatment is a combination of differentiation agents, chemotherapy and targeted therapy. This treatment combination, developed in the 1980s, transformed the condition from a fatal illness to a curable one.

Differentiation agents are non-chemotherapy treatments that help abnormal white blood cells mature (differentiate) into normal white blood cells. The non-chemotherapy treatment described below has increased the remission and cure rate to more than 95%.

Differentiation agents for APL are:

* All-trans-retinoic acid (ATRA), or tretinoin (Vesanoid®) — a form of vitamin A.
* Arsenic trioxide (ATO), a form of arsenic.

If your healthcare provider suspects you have APL, they’ll likely prescribe ATRA right away, even before tests confirm you have APL. Prompt treatment reduces the risk of life-threatening bleeding.

#### APL treatment phases

Treatment includes three phases: induction, consolidation and maintenance. Treatments vary, depending on risk:

* Induction: This phase focuses on eliminating enough leukemia cells to put APL into remission. Remission means you don’t have symptoms and tests don’t find signs of leukemia. Induction treatment uses a combination of a non-chemotherapy drug, chemotherapy and targeted therapy. You’ll need to stay in the hospital during induction, which usually lasts four to six weeks.
* Consolidation: Your oncologist may call this post-remission therapy. Consolidation treatment works to keep acute promyelocytic leukemia in remission and eliminate any remaining leukemia cells. This treatment uses the same drugs as induction treatment. You may receive treatment for eight months, with treatment sessions every two months. You may have treatment for four weeks and then a four-week treatment break. Treatment may be taking pills or receiving medication through an intravenous (IV) line.
* Maintenance: This is ongoing treatment in lower doses than induction and consolidation. Typically, people receive maintenance therapy for a year.

Your oncologist may combine treatment with supportive therapy like blood transfusions.

#### Treatment complications

The most common and serious complication is differentiation syndrome. This is a group of severe reactions to APL drugs. The reactions typically develop during the first three weeks of induction or initial treatment. Symptoms may be mild or severe and include:

* Cough.
* Excess fluid buildup around your heart and lungs (pleural effusion).
* Kidney failure (renal failure).
* Low blood pressure (hypotension).
* Low level of oxygen in your blood (hypoxemia).
* Shortness of breath (dyspnea).
* Swelling (inflammation) of your arms, legs and neck.
* Unexplained fever.
* Unexplained weight gain.

If you experience differentiation syndrome, your provider might stop treatment. They may use other drugs like hydroxyurea to bring down your white blood cell levels.

## Outlook / Prognosis

In general, the prognosis is good. While everyone’s situation is different, studies show between 90% and 95% of APL cases go into remission. APL can come back (recur) after treatment. Between 5% to 10% of people experience relapse, usually within the first three years after treatment, and need more or different treatment.

#### Survival rates

Acute promyelocytic leukemia is a rare disease, so what we know about survival rates comes from clinical trials involving people with low-risk and high-risk APL.

One analysis of clinical trials involving low-risk APL cases found that 99% of people were alive four years after treatment. Another analysis of research involving high-risk APL cases shows that 86% of people were alive after five years.

## Living With

Acute promyelocytic leukemia (APL) can come back (recur), so it’s important that you make it to your follow-up appointments.

You’ll probably have a check-up every month to two months for the first year after your treatment. After the first year, you’ll probably see your provider every three to four months for the next two years. Follow-up appointments may include tests like CBCs, PCRs and bone marrow biopsy.

#### When should I go to the emergency room?

APL can come back after treatment, causing symptoms that can get worse very quickly. If you’re in remission from acute promyelocytic leukemia, go to the emergency room right away if you have:

* Bleeding that you can’t control.
* Sudden pain and swelling in your legs or lower belly.

**DIFFERENTIAL DIAGNOSIS**

* Acute lymphoblastic leukemia (ALL)
* Acute myeloid leukemia (AML)
* Aplastic anemia
* Folic acid deficiency
* Myelodysplastic syndrome

**EPIDEMIOLOGY**

Acute promyelocytic leukemia is relatively rare and comprises about 7% to 8% of adult AML cases. Acute promyelocytic leukemia is usually seen in middle-aged people with a median age of 47 years. Acute promyelocytic leukemia occurs very rarely before the age of 20. The incidence is slightly higher in males than in females.

REFERENCES

[Acute Promyelocytic Leukemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK459352/#article-27807.s10)

[Acute Promyelocytic Leukemia (APL)](https://my.clevelandclinic.org/health/diseases/acute-promyelocytic-leukemia)

**ACUTE ERYTHROID LEUKEMIA**

**DEFINITION AND DESCRIPTION**

A rare and aggressive variety of acute leukemia known as acute erythroid leukemia (AEL) primarily affects the creation of red blood cells. The rapid proliferation of abnormal and immature erythroid precursors in the bone marrow characterizes this subtype of acute myeloid leukemia (AML), which causes impaired blood cell production and various serious symptoms. The main features of acute erythroid leukemia, including its clinical characteristics, diagnosis, treatment options, and prognosis, will be covered in this article.

## What Are the Clinical Features of Acute Erythroid Leukemia?

Individuals can differ in their clinical characteristics of acute erythroid leukemia (AEL), a rare and aggressive subtype of acute myeloid leukemia (AML).

Nevertheless, some typical AEL clinical signs and symptoms include:

* Anemia: AEL frequently results in severe anemia, characterized by weakness, exhaustion, and pallor. This happens because the production of healthy red blood cells is hampered by the proliferation of abnormal erythroid precursors in the bone marrow.
* Thrombocytopenia: AEL can lower platelet counts, increasing the risk of bleeding and making bruising more likely.
* Neutropenia: This condition, characterized by a drop in healthy white blood cells, can increase a person's susceptibility to infections.
* Fever: Some AEL patients may experience a fever, which an infection or the disease itself may bring on.
* Bone Pain: The expansion of abnormal cells in the bone marrow can cause bone pain or discomfort in places like the sternum (breastbone) and long bones.
* Chronic Fatigue: Chronic fatigue is a common sign of AEL and is frequently brought on by anemia and the overall effects of leukemia on the body.
* Spleen Enlargement (Splenomegaly): AEL can result in spleen enlargement, which can cause abdominal pain or fullness.
* Weight Loss: Unpredictable weight loss is a sign of AEL that can occasionally be observed.
* Skin Pallor: Low platelet counts and anemia can both cause the skin to appear paler.
* Infections: Neutropenia (low white blood cell count), which increases the risk of infections, increases the possibility of recurrent or severe infections in people with AEL.
* Easy Bruising and Bleeding: Thrombocytopenia (low platelet count) can cause nosebleeds, easy bleeding after minor injuries, or prolonged bleeding.
* Headaches: Some people may experience headaches, which the illness or its side effects may bring on.

## What Is the Classification of Acute Erythroid Leukemia?

Based on the classification of the World Health Organization (WHO), AEL is divided into two major subtypes:

* Erythroleukemia (EL): Erythroid precursors and myeloblasts, or immature white blood cells, are found in the bone marrow in erythroleukemia (EL).
* Pure Erythroid Leukemia (PEL): In PEL, erythroid precursors make up more than 80 percent of the bone marrow cells, even though myeloblasts only account for about 20 percent of all cells.

## Diagnosis of Acute Erythroid Leukemia

To diagnose acute erythroid leukemia (AEL), a combination of clinical assessment, lab tests, and bone marrow examination is required. The main steps in the diagnostic procedure are as follows:

* Clinical Evaluation: A detailed physical examination and medical history are frequently the first steps in the diagnostic process. Healthcare professionals will ask about symptoms, previous illnesses, and any family members with blood disorders.
* Complete Blood Count (CBC): A CBC is a blood test that tells how many different blood cell types are in the bloodstream and their total number. Anemia (low red blood cell count), thrombocytopenia (low platelet count), and abnormal white blood cell counts are the most common abnormal blood cell counts associated with AEL. An examination of a blood sample under the microscope is called a peripheral blood smear. It enables the visual evaluation of blood cell characteristics and appearance.
* Peripheral Blood Smear: The peripheral blood of people with AEL may contain abnormal white blood cells and immature erythroid precursors (erythroblasts).
* Aspiration of Bone Marrow: A slender needle takes an aspirate, or liquid sample, from the bone marrow. It is determined how many erythroid precursors and myeloblasts are present in this sample by microscopically examining it.
* Bone Marrow Biopsy: Bone and bone marrow tissue are removed in small pieces during a bone marrow biopsy using a larger needle. Additionally, a microscopic examination of this tissue sample can reveal additional details about the degree of involvement and the presence of genetic abnormalities.
* Cytogenetic and Molecular Testing: Bone marrow samples can be used for genetic analysis to help pinpoint the precise genetic anomalies connected to AEL. AEL in children, for instance, is characterized by the t(1 22) translocation linked to the RBM15-MKL1 fusion gene. Additionally, molecular profiling can reveal details about genetic mutations that could influence treatment choices.
* Flow Cytometry: Flow cytometry is a laboratory method that can be used to recognize particular cell surface markers on leukemic cells. It helps to define the subtype and type of leukemia.

## Treatment Options for Acute Erythroid Leukemia

Acute erythroid leukemia (AEL) treatment options typically involve aggressive methods to induce remission and treat the illness' symptoms:

* Chemotherapy: The mainstay of AEL treatment consists of intensive chemotherapy regimens, frequently including cytarabine and anthracycline-based medications. Chemotherapy works by removing leukemic cells from the bone marrow to induce remission.
* Stem Cell Transplantation: Allogeneic stem cell transplantation may be considered for eligible patients, especially those with high-risk characteristics or those who achieve remission but are at a high risk of relapse. The possibility of long-term disease management is provided by stem cell transplantation.
* Supportive Care: AEL treatment is incomplete without supportive care techniques like blood transfusions to treat anemia and thrombocytopenia and control infections.
* Targeted Therapies: Emerging targeted and molecularly-guided therapies might be investigated based on genetic mutations and markers unique to each case, opening up potential paths for more individualized treatment plans.

## Prognosis of Acute Erythroid Leukemia

Age, general health, and the particular subtype of AEL all affect the prognosis for the disease. AEL typically has a worse prognosis than other AML subtypes. Poorer outcomes are more common in elderly patients and those with high-risk cytogenetic abnormalities. The likelihood of relapse is high, and survival in the long term is challenging, even though treatment strategies aim to achieve remission.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Acute Erythroid Leukemia (AEL) involves distinguishing it from several hematologic and non-hematologic conditions with overlapping clinical and morphologic features. Based on current WHO classification and expert sources, here are the key differential diagnoses and considerations:

Myelodysplastic Syndrome (MDS) with Erythroid Hyperplasia

* Cases with >50% erythroid precursors but <20% myeloblasts in non-erythroid cells are classified as MDS rather than AEL.
* Prominent dysplasia in multiple lineages supports MDS diagnosis.
* MDS with excess blasts may mimic erythroleukemia but generally has a lower blast count.

## Acute Myeloid Leukemia (AML) with Myelodysplasia-Related Changes

* If >50% of myeloid or megakaryocytic lineages show dysplasia, and blasts exceed 20% of non-erythroid cells, diagnosis favors AML with myelodysplasia-related changes rather than pure erythroid leukemia.
* Cytogenetic abnormalities typical of MDS are often present.

## Pure Erythroid Leukemia (PEL)

* A subtype of AEL where the erythroid lineage predominates exclusively (>80-90%) without significant myeloblast component.
* Needs to be distinguished from reactive erythroid hyperplasia and megaloblastic anemia.

## Megaloblastic Anemia

* Can mimic AEL morphologically due to erythroid hyperplasia and dysplasia.
* Distinguished by clinical context (nutritional deficiencies), vitamin B12/folate levels, and absence of clonal proliferation.

## Other Acute Leukemias

* Acute lymphoblastic leukemia (ALL) and other AML subtypes may have overlapping features but differ in immunophenotyping and lineage markers.

## Reactive Erythroid Hyperplasia

* Non-neoplastic increase in erythroid precursors due to anemia or marrow stress.
* Diagnosis of exclusion after ruling out clonal disorders.

## Acute Megakaryocytic Leukemia

* May resemble AEL morphologically but differs by expression of megakaryocytic markers (CD41, CD61).

## Other Poorly Differentiated Malignancies

* Small blue round cell tumors or carcinomas can rarely mimic marrow infiltration; immunophenotyping helps exclude these.

REFERENCES

<https://pubmed.ncbi.nlm.nih.gov/26839191/>

<https://emedicine.medscape.com/article/199965-differential>

**ACUTE MEGAKARYOBLASTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute megakaryoblastic leukemia (AMKL) is a form of acute myeloid leukemia (AML) that occurs predominantly in childhood and particularly in children with Down syndrome (DS-AMKL). Nonspecific symptoms may be irritability, weakness, and dizziness while specific symptoms include pallor, fever, mucocutaneous bleeding, hepatosplenomegaly, neurological manifestations and rarely lymphadenopathy. Acute panmyelosis with myelofibrosis may also be associated with AMKL. In contrast to DS-AMKL (around 80 % survival), non-DS-AMKL is an AML subgroup associated with poor prognosis.

**Other Names for this Condition**

* Acute Megakaryocytic Leukemia
* AMKL (Acute Megakaryoblastic Leukemia)
* Myeloid Leukemia with Megakaryoblastic Maturation

## 

## Symptoms of Megakaryocytic Leukemia

Megakaryocytic Leukemia typically presents with symptoms related to abnormal blood cell production. Patients may experience a variety of general signs such as fatigue, easy bruising, and frequent infections. Other common symptoms include enlarged lymph nodes, unexplained weight loss, and bone pain. It is important to consult a healthcare provider for proper diagnosis and treatment if you experience these symptoms.

* Easy bruising
* Fatigue
* Frequent infections
* Bleeding gums
* Nosebleeds
* Petechiae (small red or purple spots on the skin)

## Causes of Megakaryocytic Leukemia

Megakaryocytic leukemia, also known as acute megakaryoblastic leukemia, is a rare type of leukemia that affects the blood and bone marrow. The main causes of this condition are related to genetic mutations that disrupt the normal development of blood cells, particularly megakaryocytes. These mutations can lead to uncontrolled growth and accumulation of abnormal megakaryocytic cells in the bone marrow, impairing the production of healthy blood cells.

Additionally, certain environmental factors and exposures may also play a role in the development of megakaryocytic leukemia. Early detection and prompt treatment are essential for managing this condition effectively.

* Genetic mutations
* Exposure to certain chemicals
* Radiation exposure
* Previous chemotherapy treatment
* Inherited genetic syndromes
* Viral infections

**Types of Megakaryocytic Leukemia**

Megakaryocytic Leukemia can manifest in different forms, each with its distinct characteristics. These forms may vary in terms of symptoms, prognosis, and treatment options. Understanding the types of Megakaryocytic Leukemia is crucial for proper diagnosis and management.

* **Acute Megakaryocytic Leukemia (AMKL)**: AMKL is a rare subtype of acute myeloid leukemia characterized by the excessive production of abnormal megakaryocytes in the bone marrow.
* **Chronic Megakaryocytic Leukemia**: Chronic Megakaryocytic Leukemia is a rare form of chronic myeloproliferative neoplasm where abnormal megakaryocytes accumulate in the bone marrow, leading to an overproduction of platelets.
* **Juvenile Myelomonocytic Leukemia (JMML)**: JMML is a childhood leukemia characterized by the proliferation of abnormal megakaryocytes and monocytes in the bone marrow, leading to increased production of white blood cells.
* **Myelofibrosis with Myeloid Metaplasia**: Myelofibrosis is a type of chronic leukemia where there is progressive scarring of the bone marrow leading to the overproduction of abnormal megakaryocytes and other blood cells.
* **Essential Thrombocythemia**: Essential Thrombocythemia is a chronic myeloproliferative neoplasm characterized by the overproduction of platelets by abnormal megakaryocytes, leading to an increased risk of blood clots and bleeding.

## Risk Factors

Megakaryocytic Leukemia, a rare type of blood cancer, has certain factors that can increase the likelihood of developing this condition. These risk factors are associated with specific genetic mutations or environmental exposures that can disrupt normal cell growth in the bone marrow.

Understanding these risk factors can help in early detection and management of Megakaryocytic Leukemia.

* Genetic factors
* Exposure to certain chemicals or radiation
* Previous chemotherapy or radiation therapy
* Inherited genetic syndromes
* Age, typically affecting older adults.

## Diagnosis of Megakaryocytic Leukemia

Megakaryocytic Leukemia is typically diagnosed through a series of tests and evaluations to confirm the presence of the disease. Healthcare providers may consider the patient's medical history, symptoms, and physical examination. Blood tests are commonly done to check for abnormal blood cell counts.

Additionally, bone marrow aspiration and biopsy may be performed to analyze the cells in the bone marrow. Imaging tests like X-rays or CT scans can help assess the extent of the disease. A definitive diagnosis of Megakaryocytic Leukemia is usually made based on a combination of these diagnostic procedures.

* Blood tests
* Bone marrow biopsy
* Genetic testing
* Flow cytometry
* Imaging tests (such as Xrays or CT scans)

## Treatment for Megakaryocytic Leukemia

Megakaryocytic Leukemia is a type of blood cancer that affects the production of platelets. Treatment options for Megakaryocytic Leukemia may include chemotherapy, targeted therapy, stem cell transplant, and immunotherapy. The specific treatment plan will depend on various factors like the patient's age, overall health, and the stage of the disease.

It's important for patients to work closely with their healthcare team to determine the best course of treatment for their individual situation. Early detection and prompt treatment can improve outcomes for patients with Megakaryocytic Leukemia.

* **Chemotherapy**: The primary treatment for Megakaryocytic Leukemia involves using powerful drugs to kill cancer cells and prevent their growth.
* **Stem Cell Transplant**: A stem cell transplant may be recommended to replace diseased bone marrow with healthy stem cells, allowing the body to produce normal blood cells.
* **Targeted Therapy**: Targeted therapy drugs specifically target cancer cells while minimizing damage to healthy cells, offering a more precise treatment approach for Megakaryocytic Leukemia.
* **Radiation Therapy**: Radiation therapy uses high energy beams to destroy cancer cells and may be used in combination with other treatments to manage Megakaryocytic Leukemia.
* **Supportive Care**: Supportive care measures such as blood transfusions, antibiotics, and managing symptoms like fatigue and infections play a crucial role in improving the quality of life for individuals with Megakaryocytic Leukemia.

## possible Complications of Acute Megakaryoblastic Leukemia

Acute Megakaryoblastic Leukemia (AMKL) can lead to various complications, some of which are directly related to the disease itself. In contrast, others may result from treatments or the impact of leukemia on the body. The possible complications associated with AMKL include:

* This condition can lead to bone marrow failure, where the bone marrow cannot produce enough healthy blood cells, including red blood cells, white blood cells, and platelets. This can result in anemia, increased susceptibility to infections, and bleeding tendencies
* Due to low white blood cell counts (neutropenia) caused by AMKL, patients are at a higher risk of developing infections. These infections can be bacterial, viral, or fungal and may require prompt medical intervention with antibiotics or antifungal medications
* AMKL can cause thrombocytopenia, a condition characterized by low platelet counts. This increases the risk of bleeding, manifested as easy bruising, petechiae, or prolonged bleeding from minor injuries. On the other hand, abnormal clotting may also occur in some cases
* The proliferation of abnormal cells in AMKL can lead to the enlargement of organs such as the liver, spleen, and lymph nodes (hepatosplenomegaly). This enlargement can affect organ function and may cause abdominal discomfort or pain
* In cases where there is a rapid breakdown of leukemia cells during treatment, a condition called tumor lysis syndrome may occur. This syndrome is characterized by metabolic abnormalities, such as high levels of potassium, phosphate, and uric acid in the blood, which can lead to kidney damage and other complications
* The complications of Down syndrome can include congenital heart defects, respiratory and hearing problems, thyroid conditions, and a higher risk of infections and certain types of leukemia
* Some treatments for AMKL, such as chemotherapy and radiation therapy, can increase the risk of developing secondary cancers later in life. These secondary cancers may include myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), or solid tumors

Coping with a diagnosis of Acute Megakaryoblastic Leukemia and undergoing intensive treatments can have a significant psychosocial and emotional impact on patients and their families. Supportive care, counseling, and access to mental health resources are important for addressing these aspects of the disease.

## Prevention of Acute Megakaryoblastic Leukemia

Preventing Acute Megakaryoblastic Leukemia (AMKL) primarily involves reducing known risk factors and focusing on general health and wellness practices. However, since AMKL can arise from genetic and environmental factors that may not be entirely preventable, the emphasis is often on early detection and prompt treatment. The key points regarding prevention include:

* Genetic counseling and testing can help assess the likelihood of developing AMKL in individuals with a family history of leukemia or genetic syndromes associated with an increased risk. This information may guide preventive measures or early detection strategies.
* Limiting exposure to known carcinogens such as benzene, ionizing radiation, and certain chemicals/environmental toxins may help reduce the risk of developing leukemia, including AMKL. This is particularly relevant for individuals working in industries or environments where such exposures are commonly noted
* Adopting/maintaining a healthy lifestyle that includes regular exercise, a balanced diet rich in fruits and vegetables, adequate hydration, and avoiding tobacco and excessive alcohol consumption can contribute to overall well-being and potentially reduce the risk of leukemia and other cancers
* Since AMKL can occur at any age and may not have specific early warning signs, regular health check-ups and screenings may aid in early detection. Blood tests, such as complete blood count (CBC), can sometimes detect abnormalities indicative of leukemia, prompting further evaluation and diagnosis
* Individuals with conditions known to predispose them to leukemia, such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), should receive appropriate and prompt medical management with follow-up to minimize the risk of progression to AMKL or other leukemias

Research studies and clinical trials focused on leukemia prevention, risk reduction strategies, and early intervention may offer opportunities for individuals at high risk or with specific genetic profiles to explore preventive measures or targeted therapies.

## Prognosis of Acute Megakaryoblastic Leukemia (Outcomes/Resolutions)

The prognosis of Acute Megakaryoblastic Leukemia (AMKL) can vary widely depending on various factors, including the patient's age, overall health, the presence or absence of Down syndrome, genetic characteristics of the leukemia cells, response to treatment, and presence of complications. Some key points regarding the prognosis of AMKL include:

Overall outlook:

* AMKL is generally considered a high-risk subtype of acute myeloid leukemia (AML), particularly in children and older adults
* This condition is notably more prevalent in children with Down syndrome (DS), who experience the disease with a distinct age of onset, specific genetic changes, and generally better outcomes compared to individuals without DS
* The prognosis for AMKL has improved in recent years with advances in treatment strategies, including intensive chemotherapy regimens, stem cell transplantation, and targeted therapies

Factors influencing prognosis:

* Age at diagnosis: Young children, especially those with Down syndrome (or Trisomy 21), tend to have better outcomes compared to older adults
* Genetic mutations: Specific genetic mutations or chromosomal abnormalities, such as trisomy 21 or mutations in genes like GATA1, MPL, or JAK2, can impact the prognosis and treatment response
* Response to initial treatment: Achieving remission after induction chemotherapy and maintaining that remission through consolidation therapy are favorable indicators for prognosis
* Presence of complications: Complications such as infections, organ dysfunction, or treatment-related side effects can affect overall prognosis and treatment outcomes

**Remission and relapse:**

* Many patients with AMKL achieve remission (absence of detectable leukemia cells) following initial treatment. However, the risk of relapse remains a concern, especially in high-risk cases or those with genetic abnormalities associated with poorer outcomes
* Close monitoring during and after treatment is crucial to detect any signs of relapse early and initiate appropriate interventions

**Stem cell transplantation**: For eligible patients, especially those with high-risk features or relapsed AMKL, stem cell transplantation (bone marrow or peripheral blood stem cell transplant) may offer a chance for long-term remission or cure. The success of transplantation depends on various factors, including donor compatibility and overall health status.

**Clinical trials and novel therapies:**

* Participation in clinical trials evaluating new treatment approaches, targeted therapies, or immunotherapy strategies may provide additional options for patients with AMKL and contribute to improved outcomes
* Ongoing research and advancements in understanding the molecular mechanisms of AMKL may lead to more personalized and effective treatments in the future

Long-term follow-up care is essential for monitoring treatment response, managing potential late effects or complications, and supporting overall well-being and quality of life.

Multidisciplinary care teams, including oncologists, hematologists, supportive care specialists, and psychologists, collaborate to provide comprehensive care and support throughout the treatment journey and survivorship phase.

## for Acute Megakaryoblastic Leukemia:

Children with Down syndrome (Trisomy 21) have a higher risk of developing AMKL compared to the general population. Therefore, organizations like the National Down Syndrome Society often provide resources, support, and information specifically tailored to families and individuals affected by both Down syndrome and leukemia.

**Epidemiology of Acute Megakaryoblastic Leukemia (AMKL):**

* AMKL is a rare subtype of acute myeloid leukemia (AML), accounting for approximately 3–5% of all AML cases overall
* It exhibits a bimodal age distribution with peaks in young children (especially ages 1–3 years) and in adults, often between 50 and 70 years old
* In children with Down syndrome (DS-AMKL), AMKL incidence is markedly increased—occurring about 500 times more frequently than in children without Down syndrome—and is the most common form of AML in this population
* In non-Down syndrome pediatric cases (non-DS-AMKL), AMKL accounts for about 4–15% of childhood AML cases
* In adults, AMKL represents about 1–2% of AML cases and often has a poorer prognosis compared to pediatric forms
* The overall incidence is very low, with prevalence estimated at less than 1 per 1,000,000 population.
* Demographic data from the National Cancer Database (2004–2020) show an average age at diagnosis of ~40 years, median age 51 years, with a slight male predominance (~55%) and majority of cases in non-Hispanic Whites.
* Most cases are diagnosed in urban areas and treated at academic or research cancer centers.
* AMKL can arise de novo, secondary to chemotherapy, or from progression of myeloproliferative neoplasms or myelodysplastic syndromes[1](https://pmc.ncbi.nlm.nih.gov/articles/PMC2778566/).
* Children with Down syndrome-associated AMKL generally have a better prognosis and higher survival rates (~80%) compared to non-DS-AMKL and adult AMKL, which have poorer outcomes (5-year survival ~10-40%

## Differential Diagnoses of AMKL

Minimally Differentiated Acute Myeloid Leukemia (AML M0)

* + Lacks clear lineage differentiation morphologically.
  + Negative for myeloperoxidase (MPO) but does not express megakaryocytic markers (CD41, CD61).
  + Requires immunophenotyping to distinguish from AMKL.

Acute Panmyelosis with Myelofibrosis (APMF)

* + Aggressive AML subtype with pan myeloid proliferation and prominent marrow fibrosis.
  + Can resemble AMKL due to fibrosis and immature cells but lacks megakaryocytic marker expression.

Acute Lymphoblastic Leukemia (ALL)

* + Lymphoid lineage blasts, positive for lymphoid markers (CD19, CD3), negative for megakaryocytic markers.
  + Important to distinguish due to different treatment protocols.

Pure Erythroid Leukemia (PEL)

* + Predominance of erythroid precursors; negative for megakaryocytic markers.
  + Morphologically may overlap but immunophenotyping differentiates.

Blastic Transformation of Chronic Myeloid Leukemia (CML)

* + In a blast crisis, CML can mimic AMKL; history of CML and presence of BCR-ABL fusion gene helps differentiate.
  + Often accompanied by other myeloid lineage blasts.

Idiopathic Myelofibrosis (Primary Myelofibrosis)

* + Marrow fibrosis with atypical megakaryocytes but lacks the blast proliferation seen in AMKL.
  + Clinical courses and absence of blasts differentiate it.

Metastatic Tumors in Bone Marrow (Especially in Children)

* + Solid tumor infiltration can mimic marrow infiltration by blasts.
  + Immunohistochemistry and clinical context help exclude.

REFERENCES

[Acute Megakaryoblastic Leukemia - DoveMed](https://www.dovemed.com/diseases-conditions/acute-megakaryoblastic-leukemia)

[Megakaryocytic Leukemia: Causes, Symptoms, and Treatment](https://www.medicoverhospitals.in/diseases/megakaryocytic-leukemia/)

<https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.e19023>

**CHRONIC LYMPHOCYTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Chronic lymphocytic leukemia (CLL) is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made.

The term "chronic" in chronic lymphocytic leukemia comes from the fact that this leukemia typically progresses more slowly than other types of leukemia. The term "lymphocytic" in chronic lymphocytic leukemia comes from the cells affected by the disease — a group of white blood cells called lymphocytes, which help your body fight infection.

Chronic lymphocytic leukemia most commonly affects older adults. There are treatments to help control the disease.

**Causes**

Doctors aren't certain what starts the process that causes chronic lymphocytic leukemia. What's known is that something happens to cause changes (mutations) in the DNA of blood-producing cells. A cell's DNA contains the instructions that tell the cell what to do. The changes tell the blood cells to produce abnormal, ineffective lymphocytes.

Beyond being ineffective, these abnormal lymphocytes continue to live and multiply when healthy lymphocytes would die. The abnormal lymphocytes accumulate in the blood and certain organs, where they cause complications. They may crowd healthy cells out of the bone marrow and interfere with blood cell production.

Doctors and researchers are working to understand the exact mechanism that causes chronic lymphocytic leukemia.

**Risk factors**

Factors that may increase the risk of chronic lymphocytic leukemia include:

* **Your age.** This disease occurs most often in older adults.
* **Your race.** White people are more likely to develop chronic lymphocytic leukemia than are people of other races.
* **Family history of blood and bone marrow cancers.** A family history of chronic lymphocytic leukemia or other blood and bone marrow cancers may increase your risk.
* **Exposure to chemicals.** Certain herbicides and insecticides, including Agent Orange used during the Vietnam War, have been linked to an increased risk of chronic lymphocytic leukemia.
* **A condition that causes excess lymphocytes.** Monoclonal B-cell lymphocytosis (MBL) causes an increased number of one type of lymphocyte (B cells) in the blood. For a small number of people with MBL, the condition may develop into chronic lymphocytic leukemia. If you have MBL and also have a family history of chronic lymphocytic leukemia, you may have a higher risk of developing cancer.

**Symptoms of CLL**

Many people with chronic lymphocytic leukemia have no symptoms at first. Signs and symptoms might develop as the cancer progresses. They might include:

* Enlarged, but painless, lymph nodes
* Fatigue
* Fever
* Pain in the upper left portion of the abdomen, which may be caused by an enlarged spleen
* Night sweats
* Weight loss
* Frequent infections

### When to see a doctor

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you.

**Complications of CLL**

Chronic lymphocytic leukemia may cause complications such as:

* **Frequent infections.** If you have chronic lymphocytic leukemia, you may experience frequent infections that can be serious. Sometimes infections happen because your blood doesn't have enough germ-fighting antibodies (immunoglobulins). Your doctor might recommend regular immunoglobulin infusions.
* **A switch to a more aggressive form of cancer.** A small number of people with chronic lymphocytic leukemia may develop a more aggressive form of cancer called diffuse large B-cell lymphoma. Doctors sometimes refer to this as Richter's syndrome.
* **Increased risk of other cancers.** People with chronic lymphocytic leukemia have an increased risk of other types of cancer, including skin cancer and cancers of the lung and the digestive tract.
* **Immune system problems.** A small number of people with chronic lymphocytic leukemia may develop an immune system problem that causes the disease-fighting cells of the immune system to mistakenly attack the red blood cells (autoimmune hemolytic anemia) or the platelets (autoimmune thrombocytopenia).

## 

## Diagnosis and test

### Blood tests

Tests and procedures used to diagnose chronic lymphocytic leukemia include blood tests designed to:

* **Count the number of cells in a blood sample.** A complete blood count may be used to count the number of lymphocytes in a blood sample. A high number of B cells, one type of lymphocyte, may indicate chronic lymphocytic leukemia.
* **Determine the type of lymphocytes involved.** A test called flow cytometry for immunophenotyping helps determine whether an increased number of lymphocytes is due to chronic lymphocytic leukemia, a different blood disorder or your body's reaction to another process, such as infection.  
  If chronic lymphocytic leukemia is present, flow cytometry may also help analyze the leukemia cells for characteristics that help predict how aggressive the cells are.
* **Analyze lymphocytes for genetic changes.** A test called fluorescence in situ hybridization (FISH) examines the chromosomes inside the cancerous lymphocytes to look for changes. Doctors sometimes use this information to determine your prognosis and help choose a treatment.

### Other tests

In some cases, your doctor may order additional tests and procedures to aid in diagnosis, such as:

* Tests of your leukemia cells that look for characteristics that could affect your prognosis
* Bone marrow biopsy and aspiration
* Imaging tests, such as computerized tomography (CT) and positron emission tomography (PET)

### Staging

Once a diagnosis is confirmed, your doctor uses the information about your cancer to determine the stage of your chronic lymphocytic leukemia. The stage tells your doctor how aggressive your cancer is and how likely it is to get worse quickly.

Chronic lymphocytic leukemia stages can use letters or numbers. In general, the earliest stages of disease don't need to be treated right away. People with cancer in the later stages may consider beginning treatment immediately.

**Treatment**

Your treatment options for chronic lymphocytic leukemia depend on several factors, such as the stage of your cancer, whether you're experiencing signs and symptoms, your overall health, and your preferences.

### Treatment may not be needed right away

If your chronic lymphocytic leukemia doesn't cause symptoms and doesn't show signs of getting worse, you may not need treatment right away. Studies have shown that early treatment doesn't extend lives for people with early-stage chronic lymphocytic leukemia.

Rather than put you through the potential side effects and complications of treatment before you need it, doctors carefully monitor your condition and reserve treatment for when your leukemia progresses.

Your doctor will plan a checkup schedule for you. You may meet with your doctor and have your blood tested every few months to monitor your condition.

### Treatments for intermediate and advanced stages

If your doctor determines that your chronic lymphocytic leukemia requires treatment, your options may include:

* **Chemotherapy.** Chemotherapy is a drug treatment that kills quickly growing cells, including cancer cells. Chemotherapy treatments can be administered through a vein or taken in pill form. Depending on your situation, your doctor may use a single chemotherapy drug or you may receive a combination of drugs.
* **Targeted drug therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die.
* **Immunotherapy.** Immunotherapy uses your immune system to fight cancer. Your body's disease-fighting immune system may not attack your cancer because the cancer cells produce proteins that help them hide from the immune system cells. Immunotherapy works by interfering with that process.
* **Bone marrow transplant.** A bone marrow transplant, also known as a stem cell transplant, uses strong chemotherapy drugs to kill the stem cells in your bone marrow that are creating diseased lymphocytes. Then healthy adult blood stem cells from a donor are infused into your blood, where they travel to your bone marrow and begin making healthy blood cells.  
  As new and more-effective drug combinations have been developed, bone marrow transplant has become less common in treating chronic lymphocytic leukemia. Still, in certain situations this may be a treatment option.

Treatments may be used alone or in combination with each other.

**Alternative medicine**

No alternative treatments have been proved to cure chronic lymphocytic leukemia.

### Alternative treatments for coping with fatigue

Some alternative medicine therapies may help you cope with fatigue, which is commonly experienced by people with chronic lymphocytic leukemia. Your doctor can treat fatigue by controlling the underlying causes, but often medications alone aren't enough. You may find relief through alternative therapies, such as:

* Acupuncture
* Exercise
* Massage
* Yoga

Talk to your doctor about your options. Together you can devise a plan to help you cope with fatigue.

**DIFFERENTIAL DIAGNOSIS**

* Acute Lymphoblastic Leukemia (ALL)
* Acute promyelocytic leukemia
* Diffuse large cell lymphoma
* Follicular lymphoma
* Hairy cell leukemia
* Lymphoblastic lymphoma
* Mantle cell lymphoma
* Non-Hodgkin lymphoma
* Monoclonal B-cell lymphocytosis (MBL)
* Prolymphocytic lymphoma (PLL)
* Lymphoplasmacytic lymphoma
* Histologic transformation — CLL/SLL can convert to more aggressive histology (Richter transformation), either diffuse large B cell lymphoma or Hodgkin lymphoma.

**EPIDEMIOLOGY**

CLL comprises 25 to 30% of total leukemias in the United States. According to the American Cancer Society, there will be approximately 21,040 new CLL cases and about 4,060 deaths in the year of 2020. Worldwide, 191,000 cases and 61,000 deaths are attributed to CLL/SLL every year. CLL can affect adults as young as 30 years of age. However, it is mostly seen in adults with an average age of 70 years. CLL is extremely rare in children. The incidence is known to rapidly increase with increasing age. CLL has a slightly higher incidence in male populations than female populations (1.3 to 1 to 1.7 to 1). However, studies have shown that women can have a more aggressive form of the disease than men.

The incidence of CLL varies by geographic location and race. CLL is most commonly seen in adults of the Western population. It is high amongst the Caucasian population compared to the Asian Pacific Islanders or the African-American population. The incidence of CLL in Western countries is similar to that of the United States but is rarely seen in Asian countries (China and Japan). CLL is common amongst the Jews of Eastern European descent. It is most commonly seen in Non-Hispanic Whites and least common in Asians. The incidence in African Americans is in between the Caucasian and the Asian ethnicity groups.

CLL is reported to have a genetic basis and is known to run in families (familial CLL). The age at diagnosis of the second-generation offspring is nearly 20 years younger as compared to the parent. First-degree relatives (siblings, children, or parents) of CLL patients have double the risk for CLL. Moreover, 17% of first-degree family members of CLL patients had monoclonal B cell lymphocytosis, which is a precursor of CLL. Ultimately only a small percentage of patients with monoclonal B-cell lymphocytosis (MBL) will develop into CLL.

**REFERENCES**

[Chronic Lymphocytic Leukemia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK470433/)

[Chronic lymphocytic leukemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/chronic-lymphocytic-leukemia/diagnosis-treatment/drc-20352433)

[Chronic lymphocytic leukemia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/chronic-lymphocytic-leukemia/symptoms-causes/syc-20352428)

### 

### CHRONIC MYELOID LEUKEMIA (CML)

**Definition and description**

Chronic myeloid leukemia (CML) is blood cancer that starts in the blood-forming myeloid cells or stem cells in your bone marrow. The condition has other names: chronic myelogenous leukemia or chronic granulocytic leukemia. Many people with CML may have normal life spans, thanks to therapy that has turned the condition from a life-threatening illness into a chronic illness that medication can manage.

#### How fast does CML progress or get worse?

It takes a long time for CML to get worse. You can have this condition for years before noticing symptoms. Many people learn they have CML after routine blood test results show unusual blood cell counts. Prompt treatment keeps CML from getting worse. Without treatment, chronic myeloid leukemia can become a life-threatening illness within three to four years.

## Symptoms and Causes

You can have CML without having noticeable symptoms. Chronic myeloid leukemia symptoms are mild and get worse over time. Common CML symptoms may include:

* Fatigue or weakness.
* Shortness of breath (dyspnea).
* Fever.
* Night sweats.
* Unexplained weight loss.
* Abdominal swelling or discomfort in the upper left part of your belly, where you can find your spleen.
* Feeling full when you haven’t eaten much.

### What causes chronic myeloid leukemia?

People with CML have an acquired genetic mutation or change in myeloid stem cells growing in their bone marrow. Acquired mutations aren’t present at birth and aren’t something you can inherit. Acquired mutations happen during your lifetime.

In genetic mutations, mutated or changed genes give cells new instructions on what to do. In this case, the mutation creates a new fused gene, *BCR-ABL*. The new gene triggers the following chain of events that lead to chronic myeloid leukemia:

* The *BCR-ABL* gene gives new instructions to myeloid stem cells.
* The stem cells make an abnormal version of tyrosine kinase enzymes.
* These enzymes help manage cell growth. They act like “on” and “off” switches.
* The abnormal tyrosine kinase enzymes don’t have an “off” switch.
* Without an “off” switch, myeloid stem cells in your bone marrow divide and multiply uncontrollably.
* Over time, abnormal myeloid stem cells in your bone marrow start dividing and multiplying uncontrollably, making unusually large amounts of immature white blood cells (blasts).
* Eventually, the blasts accumulate in your bone marrow, making it hard for your bone marrow to make normal red blood cells, white blood cells and platelets. You may have fewer red blood cells but more platelets and abnormal white blood cells.

#### Risk factors for CML

The only risk factor for CML is exposure to high levels of radiation — and this applies to very few people.

#### Complications of CML

People with CML may develop:

* Anemia. This condition happens when you don’t have enough red blood cells.
* Enlarged spleen (splenomegaly).

#### Can CML lead to other types of cancer?

Yes, it can. People with CML may have an increased risk of other types of cancer (second cancers). A recent study showed about 30% of people with chronic myeloid leukemia developed second cancers, including:

* Small intestine cancer.
* Thyroid cancer.
* Stomach cancer.
* Lung cancer.
* Prostate cancer.

## Diagnosis and Test

Healthcare providers may suspect you have CML if you have unusual blood test results. But they actually diagnose CML with chromosome or genetic tests that identify genetic changes or mutations. Common tests for CML include:

* Complete blood count (CBC): Providers may check for high levels of white blood cells or low red blood cell levels.
* Bone marrow aspiration or bone marrow biopsy: Providers take small samples of fluid or tissue for genetic tests. A medical pathologist will perform tests to analyze abnormal cells’ genetic makeup.
* Computed tomography (CT) scan: Providers use this test to determine if CML is affecting other parts of your body.
* Ultrasound: Providers may do this test to determine if your spleen is larger than normal. An enlarged spleen is a CML symptom.

#### What are CML stages?

Unlike many types of cancer, healthcare providers don’t characterize chronic myeloid leukemia by cancer stages. They characterize CML as being in one of four phases:

* Chronic CML:The term “chronic” often means you have a long-term condition. In CML, the term refers to the percentage of blasts (immature white blood cells) in your bone marrow and blood. In chronic CML, blasts make up about 10% of cells in your blood and bone marrow. Between 80% and 90% of people diagnosed with the condition have chronic CML. Some but not all people with chronic CML have symptoms.
* Accelerated CML:In this phase, blasts make up 10% to 19% of cells in your blood or bone marrow. Providers may also look for basophils. Basophils are white blood cells that release enzymes to improve blood flow and prevent blood clots. If you have CML, you may have increased basophil levels.
* Blast (blast crisis) CML:Blast CML can be life-threatening. In blast CML, tests show blasts make up 20% or more of cells in your bone marrow or blood. Most people with blast phase CML have very noticeable symptoms such as extreme fatigue, fever, weight loss and shortness of breath.
* Resistant CML: CML that comes back after treatment or doesn’t respond to treatment is called resistant CML.

## Management and Treatment

Healthcare providers typically treat chronic phase CML with tyrosine kinase inhibitors (TKIs). TKIs are a type of targeted therapy. In CML, the targets are the abnormal *BCR-ABL* enzymes that let abnormal white blood cells divide and multiply uncontrollably. TKIs block the enzymes so that CML cells start to die.

TKIs have made a huge difference for people with chronic myeloid leukemia. Before TKIs, only about 20% of people with the condition were alive five years after diagnosis. TKIs changed that outcome for people with early (chronic) CML.

TKIs put chronic myeloid leukemia into remission. (Remission means you don’t have CML symptoms and tests don’t find signs of the disease.) Most people take TKIs for the rest of their lives. However, recent studies show CML remains in remission even after people stop taking TKIs. This is treatment-free remission. Common TKIs to treat chronic phase CML include:

* Imatinib (Gleevec®).
* Dasatinib (Sprycel®).
* Nilotinib (Tasigna®).
* Bosutinib (Bosulif®).
* Ponatinib (Iclusig®).
* Asciminib (Scemblix®).

#### What are TKI side effects?

Side effects vary based on the specific TKI but may include:

* Stomach pain.
* Fatigue.
* Diarrhea.
* Muscle cramps.
* Edema.
* Pleural effusion (fluid accumulation around your lungs).
* Pancreatitis.
* Damage to your liver.
* Lower-than-normal white blood cell and platelet counts.

#### What are other CML treatments?

If TKIs aren’t effective, providers may use chemotherapy along with or instead of a TKI.

## Outlook / Prognosis

That depends on your situation. If treatment puts chronic myeloid leukemia into remission, you won’t have symptoms or signs of disease, but you’ll need medication to keep CML in remission. Most people with CML attend frequent, routine appointments to see how well their treatment is working.

#### What about treatment-free remission?

Treatment-free remission (TFR) means you don’t have CML symptoms or signs even after you stop taking a TKI. Recent studies show about 40% of people who stop treatment remain in remission for several years. But TFR is a relatively recent approach to treating chronic myeloid leukemia. Not everyone is a candidate. If you have chronic myeloid leukemia, it’s important that you talk to your provider before stopping treatment.

#### Is CML curable?

Right now, allogeneic stem cell transplantation is the only way to “cure” chronic myeloid leukemia. Allogeneic stem cell transplantation uses donated stem cells. It’s a complicated medical treatment. Its side effects are more serious than targeted therapy side effects. For that reason, providers typically only use stem cell transplantation to treat resistant CML.

##### CML survival rate

When you think about survival rates, it’s important to remember that survival rates can’t predict how long you’ll live. Survival rates are based on other peoples’ experiences. What was true for them may not be true for you.

That being said, overall, 90% of people with CML are alive five years after diagnosis. (Before TKI, only 22% of people with CML were alive at the five-year mark.) If you have CML, your healthcare provider is your best resource for information about what you can expect.

## Prevention

No, it can’t. Medical researchers know CML happens when a specific gene mutates, but they haven’t discovered why that mutation happens.

## Living With

If you have chronic myeloid leukemia, you may need to take medication for the rest of your life. You’ll also need regular checkups so your healthcare provider can monitor your overall health. They’ll look for signs that CML has come back and for signs of second cancers.

#### When to see a doctor

In general, you should expect to see your provider every few months for the rest of your life

## Epidemiology

The American Cancer Society (ACS) estimates that 9280 new cases of CML will be diagnosed in 2024, 5330 in males and 3950 in females. The ACS estimates that 1280 deaths from CML will occur in 2024, 750 in males and 530 in females.

The incidence of new CML cases rose on average 1.2% each year over 2012–2021, reaching 2.0 per 100,000 population in 2022. Age-adjusted death rates remained stable over 2013–2022, at 0.3 per 100,000 population per year.

CML is most often diagnosed in people aged 65-74 years. Median age at diagnosis is 66 years. CML is more common in males than in females: incidence rates per 100,000 population are 2.5 in males versus 1.5 in females.

**DIFFERENTIAL DIAGNOSIS**

## Main Differential Diagnosis of CML

## Leukemoid Reaction

* + Reactive increase in white blood cells due to infection or inflammation.
  + Unlike CML, leukemoid reaction usually has a high leukocyte alkaline phosphatase (LAP) score, no Philadelphia chromosome (Ph), and no BCR-ABL fusion gene.
  + Basophilia and eosinophilia are uncommon in leukemoid reactions.

Chronic Neutrophilic Leukemia (CNL)

* + Characterized by persistent neutrophilia without the Ph chromosome.
  + Basophils and eosinophils are typically normal, unlike in CML.
  + Mutations in CSF3R gene are often present.

Atypical Chronic Myeloid Leukemia (aCML)

* + BCR-ABL1 negative.
  + Features include leukocytosis with dysplastic neutrophils and increased immature granulocytes.
  + Lacks the Ph chromosome and BCR-ABL fusion.

Chronic Myelomonocytic Leukemia (CMML)

* + Features monocytosis (>1 x 10^9/L) with dysplastic features.
  + No Ph chromosome or BCR-ABL fusion gene.

Acute Myeloid Leukemia (AML)

* + Presence of >20% blasts in blood or bone marrow.
  + No Ph chromosome in all myeloid cells except in rare cases of Ph-positive AML.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

* + Ph chromosome present but confined to lymphoblasts, not all myeloid cells.
  + Rapid onset and different clinical courses from CML.

Other Myeloproliferative Neoplasms (MPNs)

* + Polycythemia Vera (PV): Elevated red cell mass, often with JAK2 mutation.
  + Essential Thrombocythemia (ET): Elevated platelets, JAK2 or CALR mutations.
  + Primary Myelofibrosis (PMF): Bone marrow fibrosis, anemia, splenomegaly.

Myelodysplastic Syndromes (MDS)

* + Cytopenias with dysplastic marrow features, no Ph chromosome.

**REFERENCES**

[Chronic Myelogenous Leukemia (CML): Practice Essentials, Background, Pathophysiology](https://emedicine.medscape.com/article/199425-overview#a2)

[Chronic Myeloid Leukemia (CML): Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/21845-chronic-myelogenous-leukemia-cml)

## 

## Chronic Myelomonocytic Leukemia (CMML)

**Definition and description**

Chronic myelomonocytic leukemia (CMML) is a rare type of blood cancer. Having blood cancer means that there’s a problem with how your bone marrow — the spongy tissue inside your bones — makes blood cells. With CMML, your bone marrow makes too many abnormal monocytes, a type of white blood cell. These cells can crowd out cells you need, like red blood cells, platelets and healthy white blood cells.

Doctors classify this condition as a myeloproliferative neoplasm/myelodysplastic syndrome (MPN/MDS). Here’s what this means:

* Myeloproliferative neoplasm (MPN). Your bone marrow makes *too many* blood cells. Too many of one type of blood cell can cause problems with how your blood works.
* Myelodysplastic syndrome (MDS). Your bone marrow makes *abnormal* blood cells. Instead of having mature, healthy blood cells, you may have too many immature blast cells.

CMML can range on a spectrum from slow-growing to aggressive. Your healthcare provider will explain potential treatment options that may slow its progression.

## Symptoms and Causes

CMML doesn’t always cause symptoms. The first sign of chronic myelomonocytic leukemia may be abnormal results on a blood test. When symptoms are noticeable, they usually develop gradually. CMML symptoms include:

* Fatigue or weakness (a sign of low red blood cells, or anemia)
* Frequent infections (a sign of low white blood cells, or neutropenia)
* Excessive nosebleeds or bruising easily (a sign of low platelets, or thrombocytopenia)
* Enlarged spleen (splenomegaly)
* Enlarged liver (hepatomegaly)
* Unexplained weight loss
* Night sweats
* Bone pain
* Fever

### Chronic myelomonocytic leukemia causes

Researchers don’t know what causes CMML. But they have identified several gene changes (mutations) associated with this condition. If you’re diagnosed, you’ll likely have more than one mutation. Some of the most common ones involve the following genes (with the most common listed first):

* *TET2*
* *SRSF2*
* *ASXL1*
* *RAS*

#### Risk factors

Risk factors for chronic myelomonocytic leukemia include:

* Age. Your risk increases as you get older. The median age of diagnosis is between 73 and 75. A median is a midpoint. This means half of people diagnosed are younger, and half are older.
* Sex. More males are diagnosed than females.
* Cancer treatment. About 1 in 10 people who develop CMML had previous cancer treatments like chemotherapy and radiation. Healthcare providers consider the risk of future cancers when they prescribe these treatments. They only suggest them when the benefits clearly outweigh the risks.

### Complications of CMML

In about 2 out of 10 cases, chronic myelomonocytic leukemia transforms into acute myeloid leukemia (AML). Ask your healthcare provider about your risk of developing AML based on your diagnosis and risk factors.

## Diagnosis and Tests

Your healthcare provider will consider your symptoms and ask about your medical history. They’ll perform tests to check your blood cells. Tests may include:

* Complete blood count. A monocyte count that’s too high (monocytosis) may be a sign of CMML.
* Peripheral blood smear. Monocytes that look irregular or immature (blast cells) when viewed beneath a microscope may be a sign of CMML.
* Bone marrow biopsy. Your provider may need to take a sample of bone marrow and test it in a lab to check for abnormal monocytes.
* Genetic testing. Providers also check for gene mutations associated with other blood cancers. This can help them eliminate other conditions that involve similar symptoms and blood test results.

#### Staging

Healthcare providers determine how advanced CMML is (cancer staging) based on how many blast cells you have. The stages are:

* CMML-1. Less than 4 out of every 100 cells in your blood are blasts. Less than 9 out of every 100 cells in your bone marrow are blasts.
* CMML-2. Five to 19 out of every 100 cells in your blood are blasts. Ten to 19 out of every 100 cells in your bone marrow are blasts.

The stage helps your provider decide the most effective treatment.

## Management and Treatment

First, you may need treatment to ensure you have enough healthy blood cells. You may need medications or regular blood transfusions to boost your blood cell counts. This may be a part of palliative care to help you manage symptoms.

Other treatments that target CMML directly include:

* Allogeneic stem cell transplant. This is the only treatment that can potentially cure CMML. But it’s not an option for most people. Also, it can cause life-threatening complications like graft vs. host disease.
* Chemotherapy. Chemo makes it harder for the monocytes to multiply out of control. This can provide symptom relief. Drug types include hydroxyurea and hypomethylating agents (HMA).
* Clinical trials. Your provider may recommend taking part in a clinical trial if other treatments aren’t helping. Current clinical trials are studying the effectiveness of newer CMML treatments. These include targeted therapy and immunotherapy.

### When to see a doctor

You’ll see your healthcare provider regularly (usually every one to six months). It’s important not to skip appointments. During these visits, your provider will ask about your symptoms and run blood tests. They’ll assess how your treatment is working and make adjustments as needed.

In the meantime, contact your provider if you’re experiencing unexpected or severe treatment side effects. Your provider will let you know what signs to look out for based on the treatment you’re getting.

## Outlook / Prognosis

The median life expectancy for people diagnosed with CMML is approximately between one to three years. Again, a “median” is a midpoint. This means that half of people have a shorter lifespan and half live longer. But lots of factors shape your likely outcome, or prognosis. These include:

* Blood test results. Your blood cell counts provide clues about your prognosis. Important values include your monocyte, blast cell and platelet counts. Your hemoglobin level is another important number that your healthcare provider will monitor.
* Genetic mutations. Some mutations, like mutations in the *ASXL1* gene, are associated with a worse prognosis.
* Frequency of blood transfusions. Your outcome is generally better if you don’t need repeat blood transfusions to restore your blood cells.

Your prognosis also depends on whether your condition progresses to AML. This is more likely to happen if you have CMML-2.

### Is there anything I can do to feel better?

One of the best things you can do if you have CMML is to take charge of your health in every way you can. Right now, eating nutrient-rich foods and getting enough sleep are essential. Balancing activity and rest are important, too. Connecting with others living with cancer is a good way to combat feelings of isolation that can come up. Speak to a therapist with expertise in working with people diagnosed with cancer.

Cancer can make a person feel helpless, but know that you’re still in charge of your life. And there are treatments available to help.

# Key Statistics About Chronic Myelomonocytic Leukemia (CMML)

Chronic myelomonocytic leukemia (CMML) is rare. About 1 or 2 out of every 100,000 people develop CMML each year.

* This disease occurs most often in older people, and it’s very rare in young people.
* Most people diagnosed with CMML are aged 65 years or older.
* CMML occurs more often in men than in women.

## Research into the genetics﻿ of CMML

Researchers﻿ are learning more about which changes (mutations) in the DNA inside normal bone marrow cells can cause them to develop into leukemia cells. (DNA is the substance that makes up our genes.)

Studies have found that changes in certain genes in CMML cells may help predict a person's outcome and how likely they are to go on to develop acute leukemia.

Researchers also hope that finding some of the gene changes in CMML cells might lead to treatments that target these changes (see below).

## Research into treating CMML with chemotherapy and other drugs

Studies are being done to find which chemotherapy drugs can best treat CMML, while trying to limit side effects. New drugs are being developed and tested.

As researchers have learned more about what makes cancer cells different from normal cells, they've developed drugs that target these differences. Studies are now looking at some of these targeted therapies to treat CMML. These drugs target things like specific cell signaling pathways to shut down CMML cell growth.

## Research into treating CMML with a stem cell transplant

A stem cell transplant is one of the main types of treatment for CMML, if it can be done. Scientists continue to refine stem cell transplants so that they work better and cause fewer problems. They are also looking at which patients will benefit the most and how newer transplant methods might be used to treat CMML.

**REFERENCES**

[What's New in CMML Research and Treatment? | American Cancer Society](https://www.cancer.org/cancer/types/chronic-myelomonocytic-leukemia/about/new-research.html)

[Chronic Myelomonocytic Leukemia (CMML)](https://my.clevelandclinic.org/health/diseases/chronic-myelomonocytic-leukemia-cmml)

**HAIRY CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Hairy cell leukemia is a cancer of the white blood cells. The white blood cells help fight off germs. There are a few different types of white blood cells. The white blood cells involved in hairy cell leukemia are called B cells. B cells are also called B lymphocytes.

In hairy cell leukemia, the body makes too many B cells. The cells don't look like healthy B cells. Instead, they've undergone changes to become leukemia cells. The leukemia cells look "hairy" under a microscope.

Hairy cell leukemia cells keep living when healthy cells would die as part of the natural cell life cycle. The leukemia cells build up in the body and cause symptoms.

Hairy cell leukemia often gets worse slowly. Treatment might not need to start right away. When it's needed, treatment is usually with chemotherapy.

Scientists found a type of cancer that looks like hairy cell leukemia, but it gets worse much faster. This other type of cancer is called hairy cell leukemia variant. It's considered a separate type of cancer from hairy cell leukemia, even though it has a similar name.

**Causes**

It's not clear what causes hairy cell leukemia.

Hairy cell leukemia begins in the white blood cells. The white blood cells help fight germs in the body. There are a few types of white blood cells. The white blood cells involved in hairy cell leukemia are called B cells.

Hairy cell leukemia happens when B cells develop changes in their DNA. A cell's DNA contains the instructions that tell a cell what to do. The changes tell the B cells to make a lot more B cells that don't work right. These cells go on living when healthy cells would die as part of the natural cell life cycle.

The B cells that don't work right crowd out healthy blood cells in the bone marrow and other organs. This leads to the symptoms and complications of hairy cell leukemia. For example, the extra cells can cause swelling in the spleen, liver and lymph nodes. If there isn't enough room for healthy blood cells, this can lead to frequent infections, easy bruising and feeling very tired.

**Risk factors**

The risk of hairy cell leukemia may be higher in:

* **Older adults.** Hairy cell leukemia can happen at any age. But most people diagnosed with hairy cell leukemia are in their 50s or 60s. It's rare in children.
* **Males.** Hairy cell leukemia can happen to anyone. But it's more likely in males.

**Symptoms**

Hairy cell leukemia might not cause symptoms. Sometimes a health care provider finds it by accident during a blood test for another condition.

When it causes symptoms, hairy cell leukemia might cause:

## A feeling of fullness in your belly that may make it uncomfortable to eat more than a little at a time

## Fatigue

## Easy bruising

## Recurring infections

## Weakness

## Losing weight without trying

### When to see a doctor

## Make an appointment with your health care provider if you have any persistent signs and symptoms that worry you.

## DIAGNOSIS AND TEST

## To diagnose hairy cell leukemia, your health care provider may recommend:

## Physical exam. Your provider may feel your spleen to see if it's too big. The spleen is an oval-shaped organ on the left side of the upper abdomen. If your spleen is too big you might feel a fullness in your belly. You might have pain or discomfort when you eat.

## Blood tests. You might have a blood test to measure the levels of blood cells in your blood. This test is called a complete blood count (CBC) with differential. You have three main types of blood cells in your blood. They include red blood cells, white blood cells and platelets. In hairy cell leukemia, a CBC test may show all levels of these cells are too low. Another type of blood test might involve looking at your blood under the microscope. This test can find hairy cell leukemia cells. This test is called a peripheral blood smear.

## Bone marrow biopsy. A bone marrow biopsy is a procedure to remove some of your bone marrow for testing. Your provider will remove a small amount of bone marrow from your hip area. This sample is used to look for hairy cell leukemia cells.

## Lab tests to analyze the leukemia cells. Hairy cell leukemia cells collected from your blood and bone marrow are tested in a lab. These tests look at the changes in the cells' DNA. This helps your provider understand your prognosis and what treatments are best for you.

## Computerized tomography (CT) scan. A CT scan shows detailed images of the inside of your body. Your provider may order a CT scan to look for swelling in your spleen and your lymph nodes.

## 

## Treatment

## Hairy cell leukemia treatments are good at controlling the disease. But they can't make it go away completely. Instead, treatments can control the cancer so that you can go about your life as usual. People with hairy cell leukemia can live with the disease for many years.

### Treatment might not need to start right away

## Treatment for hairy cell leukemia doesn't always need to start right away. This cancer often gets worse very slowly over time. You might choose to wait and have treatment if the cancer starts to cause symptoms.

## If you don't have treatment, you'll have regular appointments with your health care provider. You might have blood tests to see if hairy cell leukemia is getting worse.

## You might decide to start treatment if you start to get hairy cell leukemia symptoms. Most people with hairy cell leukemia will eventually need treatment.

### Chemotherapy

## Chemotherapy is a drug treatment that uses powerful drugs to kill cancer cells. It's often the first treatment for hairy cell leukemia. Chemotherapy is very effective for hairy cell leukemia. Most people get a complete or partial remission after chemotherapy. Remission means you have no signs of cancer.

## Chemotherapy for hairy cell leukemia can be given as a shot. Or it can be given as an infusion into a vein.

## If your hairy cell leukemia comes back, your provider might recommend repeating chemotherapy with the same drug or trying a different drug. Another option may be targeted drug therapy.

### Targeted drug therapy

## Targeted drug treatments attack specific chemicals present within cancer cells. By blocking these chemicals, targeted drug treatments can cause cancer cells to die.

## Targeted drug therapy is sometimes used as a first treatment for hairy cell leukemia. It can be used with chemotherapy. More often, targeted therapy is an option if the cancer comes back after chemotherapy.

## Your health care provider will have your cancer cells tested to see whether targeted drug therapy is likely to work for you.

## Alternative medicine

## No alternative medicines are helpful for treating hairy cell leukemia. Alternative medicine might be helpful in other ways. It may help you cope with the stress of a cancer diagnosis and the treatment side effects.

## Talk to your health care provider about your options, such as:

## Art therapy

## Exercise

## Meditation

## Music therapy

## Relaxation exercises

## Spirituality

## 

## Complications

Hairy cell leukemia often gets worse very slowly. Sometimes it stays stable for many years. For this reason, few complications of the disease occur.

### Too few healthy blood cells

If there are too many leukemia cells in the body, they can crowd out the healthy blood cells. That can lead to:

* **Infections.** Your body needs healthy white blood cells to fight off germs. If your body can't make enough healthy white blood cells, you might get more infections.
* **Bleeding.** Your body needs healthy platelet cells to control bleeding. If the number of platelets in your blood is low, you might notice that you bruise more easily. You might also have bleeding from the nose or gums.
* **Anemia.** Your body needs healthy red blood cells to carry oxygen through your body. Having too few red blood cells is called anemia. Anemia can make you feel very tired.

### Increased risk of other cancers

Some studies found that people with hairy cell leukemia have an increased risk of other types of cancer. The other cancers include non-Hodgkin's lymphoma, Hodgkin's lymphoma and others. It's not clear if the other cancers are caused by hairy cell leukemia or by cancer treatments.

**EPIDEMIOLOGY**

Hairy cell leukemia accounts for less than 2% of all leukemias. Its incidence is 0.3 cases per 100,000 individuals with an average male-to-female ratio of 1.5-2:1 and median age at diagnosis of 58 years. The incidence is approximately three times higher in White than in Black populations. HCL-v is estimated to be 0.2 cases per 100,000. HCL-v affects mainly elderly patients with a median age of 71 years.

REFERENCES

[Hairy cell leukemia - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hairy-cell-leukemia/diagnosis-treatment/drc-20372962)

[Hairy cell leukemia - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hairy-cell-leukemia/symptoms-causes/syc-20372956)

**MAST CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Mast cell leukemia (MCL) is a quick-progressing condition that leads to the buildup of mast cells in your bone marrow and other tissues. It falls into a group of diseases collectively known as systemic mastocytosis.

Systemic mastocytosis is rare and only affects about 13 out of 100,000 people. MCL is the rarest form of systemic mastocytosis, making up less than 1 percent of cases.

MCL can cause a variety of symptoms including low blood pressure, rashes, and itchy skin. It tends to have a poor outlook due to its rarity and lack of research on the best way to treat it.

Keep reading to learn everything you need to know about MCL, including how it differs from other types of leukemia and the latest treatment options.

## mast cell leukemia

MCL is an extremely rare condition that falls into a group of diseases known as systemic mastocytosis. Mastocytosis is a group of conditions characterized by the abnormal growth and buildup of a type of white blood cell called mast cells in your bodily tissues.

### mast cells

Mast cells are a type of white blood cell produced by your bone marrow. One of their primary functions is to release histamines and other chemicals to help fight infections. These chemicals also produce many classic allergy symptoms like excess mucus, itchiness, and swelling.

Mastocytosis can be divided into two types:

* Cutaneous mastocytosis. This is when large numbers of mast cells gather in your skin but not in other parts of your body. It’s most common in children.
* Systemic mastocytosis. This happens when mast cells gather in tissues like your skin, organs, and bones. This is the category that MCL falls into.

## Causes of mast cell leukemia

All the blood cells in your body start off as hematopoietic stem cells, also known as blood stem cells. They’re found in your bone marrow. These stem cells become one of two types of cells:

* myeloid progenitor cells
* lymphoid progenitor cells

Leukemia is a group of cancers that’s caused by cells in your bone marrow that produce abnormal or underdeveloped blood cells. Leukemias are classified based on the type of cells that are affected.

MCL is one of several types of leukemia that are caused by the abnormal growth of cells from myeloid progenitor cells. Myeloid progenitor cells can become mast cells, platelets, red blood cells, and white blood cells.

In people with MCL, at least 20 percent of mast cells in your bone marrow or 10 percent of the mast cells in your blood are abnormal. The buildup of these cells can lead to organ dysfunction that can affect your bone marrow, liver, or spleen.

It’s not entirely clear why MCL develops, but several gene mutations in the *KIT* gene are linked to the development of MCL. In about 15 percent of cases, MCL develops from a pre-existing mast cell disease.

## Symptoms of mast cell leukemia

The following are symptoms among patients with mast cell leukemia may experience:

* lethargy and weakness
* fainting
* flushing
* fever
* fast heart beat (tachycardia)
* losing more than 10 percent of body weight
* diarrhea
* nausea and vomiting
* loss of appetite
* itchy skin blisters
* bone pain

## Diagnosis and test

MCL most commonly occurs in adults. Half of people with MCL are over age 52, but some as young as 5 years old have been described in the medical literature.

A diagnosis for mast cell leukemia requires you to:

* meet the criteria for systemic mastocytosis
* show signs of organ damage
* have at least 20 percent atypical mast cells in your bone marrow or ten percent in your blood

For a systemic mastocytosis diagnosis, the World Health Organization’s criteria require you to meet the major criterion or at least three minor criteria.

#### Major criterion

* clusters of at least 15 mast cells in bone marrow biopsies

#### Minor criteria

* more than 25 percent of mast cells are atypical measure in bone marrow
* *KIT* gene mutation at codon 816 in bone marrow or other internal organs
* mast cells exhibit CD2 or CD25
* baseline serum tryptase level greater than 20 ng/mL

To diagnose systemic mastocytosis and MCL, an oncologist will likely order a bone marrow biopsy. This is when a small tissue sample is taken with a long needle, often from your hip bone. The doctor may also take a biopsy of other affected organs.

Medical professionals can use your biopsy sample to look for certain genes that are common in people with MCL. They’ll run tests to assess the density and appearance of your mast cells.

A blood test may be ordered to search for markers of MCL like:

* low red blood cell count
* high histamine levels
* low platelet levels
* high white blood cell count
* low albumin levels
* high tryptase level

**Treatment**

There’s no standard therapy for MCL due to the rarity of the disease and lack of research. Also, no one particular treatment has shown consistently effective results.

Treatment may include medications known as monoclonal antibodies, tyrosine kinase inhibitors, and forms of chemotherapy used to treat acute myeloid leukemia.

Allogeneic bone marrow transplants are also sometimes needed. This procedure involves transplanted bone marrow stem cells from a donor to replace cells damaged by chemotherapy.

## outlook for people with MCL

The outlook for MCL is generally poor. About half of people who develop MCL live less than 6 months from the time of diagnosis. MCL often leads to multiorgan failure or anaphylactic shock due to the buildup of mast cells.

Despite the poor prognosis, some people have a better result. The man in the 2017 case study went into full remission after receiving treatment, and some people’s disease progresses slower than predicted.

### Staying hopeful

The diagnosis and treatment process for leukemia can be overwhelming for anyone. However, it’s important to remember that you are not alone and new treatments are being studied.

As researchers continue to learn about MCL, treatment will likely become more refined in the future, and it’s possible the outlook of the disease will improve.

**DIFFERENTIAL DIAGNOSIS**

## Myelomastocytic Leukemia (MML)

* A rare myeloid neoplasm characterized by increased immature mast cells/metachromatic blasts (≥10%) in bone marrow, usually in the context of advanced myeloid neoplasms such as AML or MDS.
* Distinguishing features:
  + MML lacks systemic mastocytosis (SM) diagnostic criteria (no compact mast cell aggregates).
  + Mast cells in MML are CD25-negative and typically lack KIT mutations.
  + MCL mast cells are CD25-positive and usually harbor KIT mutations (especially D816V).
  + MCL requires ≥20% atypical/immature mast cells in marrow; MML requires ≥10%.
* MML is considered a distinct entity and may be underdiagnosed without routine tryptase and CD117 staining.

Aggressive Systemic Mastocytosis (ASM)

* A form of systemic mastocytosis with organ damage but <20% mast cells in marrow.
* MCL is considered a leukemic variant of SM with ≥20% mast cells in marrow.
* ASM and MCL share KIT mutations and CD25 positivity but differ in mast cell burden and clinical aggressiveness.

Acute Basophilic Leukemia (ABL)

* Characterized by blasts with basophilic granules that may express tryptase and CD25 but typically lack CD117 expression.
* Serum tryptase levels are only mildly elevated compared to MCL.
* ABL blasts express basophil-specific markers (e.g., BB1, 2D7) which are absent in MCL.

Chronic Basophilic Leukemia (CBL)

* Features mature or hypogranulated basophils expressing tryptase but not CD117.
* Peripheral blood basophilia is prominent, unlike in MCL.

Tryptase-Positive Acute Myeloid Leukemia (T+ AML)

* AML subtype with elevated serum tryptase and some tryptase expression on blasts.
* Unlike MCL, blasts are CD34-positive and CD117-negative or weak, and CD25 is absent.

Other Acute Leukemias

* All other acute leukemias (AML, ALL) should be excluded via immunophenotyping and genetic testing.

**EPIDEMIOLOGY**

Epidemiology of Mast Cell Leukemia (MCL):

* MCL is an extremely rare and aggressive subtype of systemic mastocytosis (SM), representing about 1% of all SM cases and approximately 4% of advanced SM cases.
* The prevalence of MCL is estimated at less than 1 per 1,000,000 people globally, making it one of the rarest hematologic malignancies.
* Studies report a median age at diagnosis ranging from 52 to 63 years, with cases documented from adolescence (as young as 5 years) to elderly (up to 90 years).
* Gender distribution varies:
  + Some studies show a female predominance (female:male ratio ~1.5:1)
  + Other data, such as from the National Cancer Database (NCDB), indicate a slight male predominance (~53% males).
* Most patients are White and non-Hispanic, with the majority residing in metropolitan areas and treated at academic or research centers.
* MCL can present as primary (de novo) in about 70% of cases or as secondary (following other forms of mastocytosis) in around 30%.
* Clinical presentation involves multi-organ involvement including bone marrow, liver, spleen, gastrointestinal tract, and others.
* The 5-year overall survival rate is very poor, approximately 16.6%, reflecting the aggressive nature of the disease.
* Incidence trends show a gradual increase in diagnosis over time, likely due to improved awareness and diagnostic method

REFERENCE

<https://pmc.ncbi.nlm.nih.gov/articles/PMC10046872/>

<https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.e19049>

[Mast Cell Leukemia: Symptoms, Treatment, and Outlook](https://www.healthline.com/health/leukemia/mast-cell-leukemia)

**AGGRESSIVE NATURAL KILLER CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Aggressive natural killer (ANK) cells belong to a group of white blood cells called “lymphocytes” which play a vital role in the body’s immune system. NK cells in particular target and destroy disease-causing pathogens, and detect and control the early signs of cancer.

In ANKL, the NK cells are unable to perform their usual functions. The accumulation of cancerous or “neoplastic” NK cells in the body leads to serious and life threatening complications.

## Symptoms of ANKL

ANKL can present differently from person to person. However, the most common signs and symptoms include:

* fever
* night sweats
* unintentional weight loss
* swelling of the lymph nodes

People with ANKL commonly present with a rare and life threatening inflammatory condition called “fulminant hemophagocytic lymphohistiocytosis (HLH). This condition occurs as a result of immune system overactivation, and can lead to multiple organ failure. Common HLH triggers include:

* infection, with Epstein-Barr virus (EBV), which is the most common cause
* acute illness
* cancer

The two most common clinical features of HLH are fever and enlargement of the spleen (splenomegaly). The latter may cause symptoms such as:

* abdominal discomfort
* pain in the upper left abdomen
* referred pain in the upper left shoulder
* abdominal bloating
* feeling full after eating very little (early satiety)
* weight loss

## Causes and risk factors of ANKL

Due to the rarity of NKL, scientists are still working to determine its causes and risk factors.

While anyone can develop ANKL, the average age at disease onset is 40 years, and the disease is more common among people of Asian ethnicity.

EBV infection is a risk factor for ANKL. As the Centers for Disease Control and Prevention (CDC) explains, EBV is among the most common human viruses in the world, and most people develop EBV at some point in their lifetime. Children rarely experience symptoms, while teenagers and adults may experience symptoms for several weeks or months.

### The role of Epstein-Barr virus in ANKL

Once a person has had EBV, the virus becomes inactive or “latent” in their body. However, the virus can express viral proteins that disrupt cell functioning, suppress cell death, and trigger uncontrolled cell growth. This, in turn, can increase the risk of certain cancers.

Cases of ANKL that are associated with EBV infection are referred to as “EBV-positive”.

ANKL can also develop in people who have never had EBV. Doctors refer to this type of ANKL as “EBV-negative”. Unlike EBV-positive ANKL, EBV-negative ANKL occurs most often in older adults and arises equally among people of Asian and non-Asian ethnicity.

However, EBV-positive and EBV-negative ANKL appear equally aggressive in terms of their clinical onset and disease course.

## Diagnosis and test

Doctors may have difficulty accurately diagnosing ANKL due to the following:

* The disease is rare and has a rapid onset.
* The disease has no specific pathologic features and shares symptoms with many other conditions.
* The disease has no standard immunophenotypic features, meaning that the diseased cells do not show any features specific to ANKL, such as specific antigens or markers on their surface.

ANKL can be particularly difficult to diagnose in its early stages due to the small number of cancerous NK cells in the bone marrow. According to some studies, this number may be as low as 5% or even less.

As the disease progresses, the number of cancerous NK cells in the bone marrow rapidly increases. As such, the reviewers recommend that doctors conduct multiple blood or bone marrow specimens at various time points to check for the disease.

Once doctors have retrieved a blood or bone marrow sample, they will send it to a lab for analysis using flow cytometry. This analysis helps determine the types of cells, their characteristics, and the presence of tumor markers.

## Treatment for ANKL

Treatment for ANKL typically involves chemotherapy, radiation therapy, or a combination of the two. Large-scale clinical studies are necessary to determine the optimal treatment approach. A person with ANKL can consider talking with their doctor about the possibility of joining clinical trials.

Combined radiation therapy and chemotherapy regimens incorporating the chemotherapy drug “L-asparaginase” appear most effective for treating ANKL. An example of such a regimen is the “SMILE” regimen, which consists of the following drugs:

* dexamethasone
* methotrexate
* ifosfamide
* L-asparaginase
* etoposide

## outlook for ANKL

The outlook for ANKL is typically very poor, even among individuals on the more successful treatment regimens, such as SMILE.

In a small, older study from 2016, only 50% of 13 individuals on the SMILE regimen experienced a partial or complete response to treatment, with only 27.8% experiencing a complete response to treatment. Eight individuals then received a follow-up blood and bone marrow transplant called “hematopoietic stem cell transplantation (HSCT)”, which involves implanting stem cells to promote healthy blood cell production. Six individuals remained alive following the procedure.

A 2017 study of 21 people with ANKL also demonstrated improved survival rates among those who received HSCT following their initial treatment. Of the 17 individuals who received an L-asparaginase-containing regimen, 14 experienced a complete treatment response prior to HSCT.

At 25-month follow-up, the 2-year progression-free survival (PFS) was 20%, and the overall survival (OS) was 24%. The term “PFS” refers to the length of time a person lives with a disease without it worsening, while the term “OS” refers to the average length of time a person lives following their initial diagnosis.

**EPIDEMIOLOGY**

Epidemiology of Aggressive NK-Cell Leukemia (ANKL):

* ANKL is a very rare and highly aggressive hematologic malignancy derived from natural killer (NK) cells.
* It predominantly affects young to middle-aged adults, with a median age at diagnosis typically between 30 and 40 years.
* There is a marked geographic and ethnic predilection, with the highest incidence reported in East Asia (especially Korea, Japan, and China) and parts of Central and South America.
* ANKL is extremely rare in Western countries, with only sporadic cases reported.
* The disease shows a slight male predominance.
* Due to its rarity, precise incidence and prevalence data are limited, but it is estimated to account for less than 1% of all leukemias.
* ANKL is strongly associated with Epstein-Barr virus (EBV) infection, which is detected in the leukemic NK cells in most cases, especially in endemic areas.
* The disease has a rapid clinical course, often presenting with systemic symptoms, hepatosplenomegaly, and bone marrow failure.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Aggressive NK-Cell Leukemia (ANKL) includes several hematologic malignancies and related disorders with overlapping clinical, morphologic, immunophenotypic, and genetic features. Based on the latest expert sources, the key differential diagnoses are:

Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKTL)

* Shares many immunophenotypic and morphological features with ANKL, including strong association with Epstein-Barr virus (EBV) infection and expression of NK-cell markers (CD2, CD56, cytoplasmic CD3ε).
* ENKTL typically involves the upper aerodigestive tract (nasal cavity, nasopharynx) but can disseminate to other organs including bone marrow.
* Clinical presentation is generally less aggressive than ANKL.
* Genetic differences: ANKL often shows gains of 1q and losses of 7p15.1-p22.3 and 17p13.1, which may help distinguish it from ENKTL.

## Chronic Lymphoproliferative Disorder of NK Cells (CLPD-NK)

* Indolent NK-cell proliferation without EBV association.
* Characterized by uniform CD8 positivity and loss of CD2 expression, unlike ANKL.
* Clinical course is much less aggressive; many patients are asymptomatic or have mild cytopenias.

## EBV-Associated Hemophagocytic Lymphohistiocytosis (EBV-HLH)

* A severe hyperinflammatory syndrome triggered by EBV infection, often with expansion of T or NK cells.
* Can mimic ANKL clinically with fever, hepatosplenomegaly, cytopenias, and coagulopathy.
* Distinguishing features include lack of clonal NK-cell proliferation and absence of neoplastic NK cells on flow cytometry or biopsy.

## Systemic EBV-Positive T-Cell Lymphoma of Childhood

* Aggressive EBV-driven T-cell lymphoma presenting with systemic symptoms and HLH, mainly in children.
* Immunophenotype shows T-cell markers rather than NK-cell markers.

## Primary Effusion Lymphoma (PEL)

* A rare lymphoma presenting as effusions without tumor masses, sometimes involving NK cells.
* Distinguished by presence of HHV-8 infection and lack of EBV association in many cases.

## Other NK-Cell Neoplasms

* Blastic NK-cell lymphoma/leukemia (rare) and other mature NK-cell neoplasms need to be considered.

Reference

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7600035/>

[NK cell leukemia (ANKL): Symptoms, causes, and treatment](https://www.medicalnewstoday.com/articles/nk-cell-leukemia#:~:text=However%2C%20the%20most%20common%20signs%20and%20symptoms%20include%3A,weight%20loss%204%20swelling%20of%20the%20lymph%20nodes)

### Lymphoma

**Definition and description**

Lymphoma affects the lymphatic system, where abnormal lymphocytes multiply in lymph nodes, weakening immunity. It accounts for about half of blood cancer cases annually

Lymphoma is a cancer of the lymphatic system. The lymphatic system is part of the body's germ-fighting and disease-fighting immune system. Lymphoma begins when healthy cells in the lymphatic system change and grow out of control.

The lymphatic system includes lymph nodes. They are found throughout the body. Most lymph nodes are in the abdomen, groin, pelvis, chest, underarms and neck.

The lymphatic system also includes the spleen, thymus, tonsils and bone marrow. Lymphoma can affect all these areas and other organs in the body.

Lymphoma” is the general term for cancer in your lymphatic system — the network of tissues, vessels and organs that help your body fight infection. It’s considered a blood cancer because the condition starts in white blood cells (lymphocytes) in your lymphatic system.

There are many types of lymphoma. The main subtypes are:

* Hodgkin lymphoma (formerly called Hodgkin disease).
* Non-Hodgkin lymphoma.

Many treatments for lymphoma exist. The treatment that's best for you will depend on the type of lymphoma you have. Treatments can control the disease and give many people with lymphoma the chance of a full recovery.

## Stages

* Stage 1 : In this stage, the lymphoma only affects a single group of lymph nodes (glands). It can occur anywhere in the body, above or beneath the diaphragm, and not just in the neck.
* Stage 2 : It is the advanced stage of lymphoma. The term "advanced lymphoma" refers to lymphoma originating in the lymph nodes and progressing to at least one organ outside the lymphatic system, such as the bone marrow, lung, and liver.
* Stage 3 : At least two groups of lymph nodes have lymphoma. These may be located everywhere on the body. However, they are located on the same side of the stomach to be classified as stage 2 lymphoma.
* Stage 4 : In this stage, the lymph nodes affected by lymphoma are located on both sides of the stomach.
* Stage 5 : The lymphoma spreads to one or more groups of lymph nodes and originates in a single organ (except the lymphatic system). It must be on the single side of the stomach.

### Signs and symptoms

### of lymphoma may include:

Many lymphoma symptoms are like symptoms of other, less serious diseases. Having these symptoms doesn’t mean that you have lymphoma. But you should consider talking to a healthcare provider whenever you have changes in your body that don’t go away within a few weeks.

Symptoms common to Hodgkin lymphoma and non-Hodgkin lymphoma can include:

* Painless swelling of one or more lymph nodes in your neck, armpits or groin that doesn’t go away within a few weeks.
* Persistent fatigue, when you feel very tired day after day even after getting enough sleep.
* Fever stays above 103 degrees Fahrenheit (39.5 degrees Celsius) for more than two days, or a fever that comes back.
* Drenching night sweats, sweating that are so intense that you wake up to find your pajamas and sheets soaking wet.
* Shortness of breath (dyspnea), when you feel as if you can’t get enough air in your lungs.
* Unexplained weight loss, when you’ve lost 10% of your total body weight over six months without dieting or exercise.

### Causes of lymphoma

Lymphoma happens when the white blood cells in your lymphatic system change (mutate) into rapidly growing cancer cells that don’t die. Like most cancers, the majority of the genetic mutations that cause lymphoma happen spontaneously, without an identifiable cause. But research suggests the following conditions or issues may increase your risk of developing lymphoma:

* You have or have had viruses including HIV (human immunodeficiency virus), Epstein-Barr (mononucleosis) and Kaposi sarcoma human immunodeficiency virus.
* You have a family history of lymphoma.
* Your immune system is weakened by other conditions or medical treatments. For example, people who have organ transplants take immunosuppressant medication to keep their bodies from rejecting the transplanted organ.
* You have an autoimmune disease. An autoimmune disease happens when your immune system accidentally attacks your body instead of protecting it.

Healthcare professionals aren't sure what causes lymphoma. Lymphoma begins with changes in the DNA of a disease-fighting blood cell called a lymphocyte.

A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. Healthy cells die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make more cells quickly. The cancer cells can go on living when healthy cells die.

In lymphoma, the DNA changes happen in the lymphocytes. The changes can:

* Lead diseased lymphocytes grow out of control.
* Cause too many diseased lymphocytes in the lymph nodes.
* Cause the lymph nodes, spleen and liver to swell.

## Risk factors

Some factors can increase the risk of lymphoma. They include:

* **A weakened immune system.** If the immune system is weakened by medicines or illness, there might be a higher risk of lymphoma. People with a weakened immune system include those taking medicines to control the immune system, such as after an organ transplant. Certain health conditions, such as infection with HIV, also can weaken the immune system.
* **Family history.** People who have a parent, sibling or child with lymphoma are at higher risk of the disease.
* **Specific infections.** Some infections increase the risk of developing lymphoma. Examples include Epstein-Barr virus, Helicobacter pylori and HIV.
* **Your age.** Some types of lymphoma are more common in teens and young adults. Others happen more often in people over 55.

**Treatment**

The treatment for lymphoma depends on age, type of lymphoma, stage of lymphoma, and overall health of the patient. The different methods used for the treatment of lymphoma are:

* **Surgery**:The surgery aims to remove the affected spleen and lymph nodes as much as possible. It is usually performed in early-stage lymphoma.
* Bone marrow transplant:In this, a high dose of chemotherapy or radiation are given to kill the lymphoma and suppress the bone marrow. The destroyed bone marrow is later replaced with healthy stem cells.
* Radiation therapy:Radiation therapy is usually more effective on lymphoma cells than any other type of cancer cells, as lymphoma cells are sensitive to radiation. It is used to treat early-stage lymphoma that is confined to one part of the body. In this, high-powered beams are used to kill the cancerous cells. Radiation therapy may be combined with surgery or chemotherapy when the tumor is very bulky and is not removed (by surgery) or killed (by chemotherapy).
* **Chemotherapy**:Chemotherapy involves using drugs that kill the lymphoma cells by interfering in cell division. Chemotherapy is also used in relieving the symptoms in patients with advanced lymphoma as a part of palliative care.
* Immunotherapy:Immunotherapy enables the immune system to recognize unique proteins on the surface of lymphoma and attack them. These drugs also strengthen the immune system.
* **Targeted therapy**:Targeted therapy targets the abnormalities or weaknesses of the lymphoma cells and targets them. It attacks the lymphoma cells more precisely than chemotherapy and causes less damage to the healthy cells.

## Prevention

The risk of lymphoma can be reduced by:

* Maintaining a healthy BMR
* Avoiding activities that increase the chance of getting infected with AIDS and hepatitis C
* Avoiding unnecessary exposure to harmful chemicals and radiation, as overexposure to industrial and agricultural chemicals enhances the risk of lymphoma
* Getting regularly screened after the age of 50
* Quitting smoking
* Following a healthy eating pattern
* Being physically active

### Prognosis of Lymphoma

### The five-year survival rate describes the percentage of people who live at least five years after being diagnosed with a particular type of cancer.According to the American Cancer Society, the overall five-year survival rate for NHL is 74 percent. It’s important to note that these figures are variable for each subtype of NHL. The five-year relative survival rate for people with localized Hodgkin lymphoma is about 93 percent. It’s about 83 percent for those with distant-stage disease (when the cancer has spread to areas such as the lungs, liver, or bone marrow). The survival rates have steadily improved for this type of cancer in recent years. Hodgkin lymphoma is now considered one of the most curable forms of cancer. It’s important to remember that survival rates are only estimates. Your outlook will depend on several factors, including the type of lymphoma you have and how aggressive your disease is, as well as your age and general health.

## Duration of Lymphoma

While treatment for lymphoma is often successful and leads to complete remission, for some patients, lymphoma may be a chronic illness. The cancer doesn’t go away, but with ongoing treatment and close monitoring, it can be controlled and might not grow or spread for months or years.

**Treatment and Medication Options for Lymphoma**

Treatment options are different for Non-Hodgkin Lymphomas and Hodgkin Lymphomas. And treatment will also depend on the stage of the cancer, among other factors.

## Complications of Lymphoma

Treatments for Hodgkin and non-Hodgkin lymphoma are now so varied and effective that many patients will be cured and live long lives after diagnosis and treatment. But there can be complications as a result of treatment. Depending upon the type of treatment and the health of the patient, doctors will watch for heart disease, secondary cancers (elsewhere in the body), lung and bone health, and cognitive and memory problems. Regular follow-up care is essential.

**Epidemiology**

In 2020, over 101,133 cases and over 32,560 deaths occurring from HL were reported globally by GLOBOCAN in 2018, and this malignancy can be cured in most cases . The outstanding characteristic expression of this malignancy occurs in approximately ≤1% of neoplasm . It is estimated that approximately ≤ 1 of 25,000 people are affected by this cancer annually and accounts for about 1% of all cancers that occur in the world. According to IARC, GLOBOCAN , the occurrence of Hodgkin lymphoma is 2.7-2.8 per 100,000 persons annually (2.44/100,000 persons in Nigeria), however this varies considerably by age, gender, ethnic groups, geographical regions and socio-economic status . Also recent statistics of IARC, GLOBOCAN estimates 79,990 i.e. 0.4% incidence with mortality of 26,167 i.e. 0.3% cancer incidence globally . There has been an upsurge in the incidence trend of Hodgkin lymphoma. Studies from GDB reveal data on the rise in rates of HL from 72,937 to 101,133 cases and mortality of 35,946 to 32,560 between 1990-2017 . HL is an unusual neoplasm, with 7000-7500 new diagnoses yearly in the United States and United Kingdom and majority of the affected people are diagnosed at the early occurrence of the disease .

In Nigeria, about 2030 cases were diagnosed in 2020 and a 5-year prevalence of 5031. Also in the Mediterranean basin populations such as France and Italy, incidence rates are estimated at 2.51 male to 2.74 female and 2.76 male to 2.02 female, respectively with mortality occurrence at 0.29 and 0.37 respectively , whereas incidence and mortality in Nigeria is estimated at 1.6% and 1.2%, the mortality is about 4 times the risk of death in other regions . HL can affect individuals of any age, however, occurs frequently between two age groups specifically i.e. 15-35 and above 55 years respectively. Generally occurrence of lymphomas in Africa is very minimal including association of risk factors such as HIV. HL incidence in Nigeria is similar to the incidence in other regions but there is a higher death rate in Nigeria, hence this review focuses on HL in Nigeria to review the clinical patterns, trends and contributory factors to the incidence of HL and how this can be overcome. HL ranked the 12th most common cancer in Nigeria with 2030 new cases and 919 deaths reported in 2020 . We reviewed briefly other reported studies on incidence, clinicopathological features and frequency of occurrence of Hodgkin lymphoma. A 25 year review of cases seen at the University of Benin teaching hospital presents a dual-peak occurrence of HL between 11-15 and 21-25 years respectively as well as a statistically significant difference between age and gender distribution. Olu-Eddo reported 56 (6.8%) cases of HL, most of which were mixed cellularity HL subtype (64.3%) and lymphocyte depleted HL (19.6%). A fifteen-year epidemiological study of histopathological examination of lymphomas conducted in Ibadan showed that the lymphoma was identified in 51 males and 29 females between ages of 5 - 74 years and about 60% occurred in ages below 40 while modal group occurrence was in their thirties. Sites of occurrence were frequent at a nodule and others occurring at several nodal sites, such as intestine, liver, and spleen . A case study in the north east region of Nigeria evaluating lymphomas in 50 cases studied the patterns of presentations relative to sex, stating that 10 cases were of Hodgkin lymphoma with ratio 4:1 male and female respectively. Patterns of presentations revealed the following; 4 cases in stage II, 3, 2 and 1 were diagnosed to be I, III, and IV stages of HL respectively . In Ile-Ife, of eighty-three histological samples of lymphoma cases, about 20.5% were identified as cHL, presenting frequently the cellular mixture subtype and eleven cases were observed to be associated with Epstein Barr virus . Kolawole in a recent study on histological assessment of samples retrieved from different laboratories in Lagos, conducted in LUTH, indicated a sudden rise in incidence of HL. Thirty cases were identified as HL, two were marked as NLPHL, HL subtypes; NSHL, MCHL AND LRHL were estimated at 40%, 23.3%, and 10%, respectively above 7 years. This malignant disease displays a bimodal curve of its occurrence in more advanced nations. Also, the occurrence rate is said to be stable for over twenty years . In the less advanced nations, the entire occurrence of Hodgkin lymphoma is lesser when compared to advanced nations excluding children below 15 years, where a higher occurrence is observed. Just a slight raised level of occurrence is observed throughout adolescence and young adulthood . Generally the malignant neoplasm has been identified to persist more in males compared to females. In 2010, Worldwide it resulted in approximately 18,000 deaths downward from 19,000 deaths in 1990 . Another recent re-classified lymphomas cases from formalin fixed paraffin embedded tissues using WHO classification, and reports higher male to female ratio, ethnic variations in the lymphoma cases; CLL was prevalent in the Hausa compared to HL in the Yoruba ethnic while the Igbo ethnic group reported similar distribution of CLL, HL, and diffuse large B-cell lymphomas not otherwise specified (DLBCL, NOS).

## Diagnostic Considerations

Other conditions to consider in the differential diagnosis of Hodgkin lymphoma include the following:

* Any disease presenting with lymphadenopathy and constitutional symptoms
* Infection with human immunodeficiency virus (HIV)
* Hypersensitivity reaction
* Other solid tumors
* Non-Hodgkin lymphoma, particularly diffuse large B cell lymphoma and anaplastic large cell lymphoma, both of which may have CD30 expression

Because Hodgkin lymphoma is considered a curable malignancy and the differential diagnosis is broad, medicolegal problems may arise from failure to diagnose the disease in a timely manner, possibly due to the following factors:

* The misinterpretation of B symptoms
* A lack of follow-up for abnormal chest radiographs or physical examination findings
* A missed pathologic diagnosis because a needle biopsy was obtained rather than an excisional lymph node biopsy

Occasionally, Hodgkin lymphoma can present as hemophagocytic syndrome (hemophagocytic lymphohistiocytosis).The hemophagocytic syndrome may be more prevalent in patients with Epstein-Barr virus (EBV) antigen expression and has the following characteristics:

* Pancytopenia
* Fever
* Hepatosplenomegaly with liver function test abnormalities
* Elevated serum levels of ferritin and triglycerides
* Phagocytosis of hematopoietic lineage cells by benign macrophages

## Differential Diagnoses

* Cytomegalovirus (CMV)
* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Non-Hodgkin Lymphoma (NHL)
* Physical Medicine and Rehabilitation for Systemic Lupus Erythematosus
* Sarcoidosis

**References**

1. Bower M, Waxman J (2015) Lecture Notes: Oncology. John Wiley & Sons.

2. Küppers R, Hansmann ML (2005) The Hodgkin and Reed/Sternberg cell. Int J Biochem Cell Biol 37(3): 511 517.

3. Aggarwal P, Limaiem F (2019) Reed Sternberg Cells. In StatPearls. StatPearls Publishing. 4. Gobbi PG, Ferreri AJM, Ponzoni M, Levis A (2013a) Hodgkin lymphoma. Crit Rev Oncol Hematol 85(2): 216 237.

5. Re D, Ku R, Diehl V (2005) Molecular Pathogenesis of Hodgkin’s Lymphoma. J Clin Oncol 23(26): 6379-6386.

6. Gobbi PG, Ferreri AJM, Ponzoni M, Levis A (2013b) Hodgkin lymphoma. Crit Rev Oncol Hematol 85(2): 216 237.

7. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the committee on Hodgkin’s disease staging classification. Cancer Res 31(11): 1860 1861.

8. Poppema S (2005) Immunobiology and pathophysiology of Hodgkin lymphomas. Hematology Am Soc Hematol

<https://www.americanoncology.com/cancer-we-treat/prevention/lymphoma-cancer>

[Lymphoma - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/lymphoma/symptoms-causes/syc-20352638)

[Lymphoma: Symptoms, Causes and Treatment](https://my.clevelandclinic.org/health/diseases/22225-lymphoma)

**HODGKIN LYMPHOMA**

**DEFINITION AND DESCRIPTION**

Hodgkin lymphoma is a type of cancer that affects the lymphatic system. The lymphatic system is part of the body's germ-fighting and disease-fighting immune system. Hodgkin lymphoma begins when healthy cells in the lymphatic system change and grow out of control.

The lymphatic system includes lymph nodes. They are found throughout the body. Most lymph nodes are in the abdomen, groin, pelvis, chest, underarms and neck.

The lymphatic system also includes the spleen, thymus, tonsils and bone marrow. Hodgkin lymphoma can affect all these areas and other organs in the body.

Hodgkin lymphoma, which used to be called Hodgkin disease, is one of two broad types of lymphoma. The other is non-Hodgkin lymphoma.

Advances in diagnosis and treatment of Hodgkin lymphoma have helped give people with this disease the chance for a full recovery.

**Causes**

Healthcare professionals aren't sure what causes Hodgkin lymphoma. It begins with changes in the DNA of a disease-fighting blood cell called a lymphocyte. A cell's DNA contains the instructions that tell the cell what to do.

The DNA changes tell the cells to multiply quickly and live when other cells would naturally die. The Hodgkin lymphoma cells attract many healthy immune system cells to protect them and help them grow. The extra cells crowd into the lymph nodes and cause swelling and other symptoms.

There are multiple types of Hodgkin lymphoma. The type of lymphoma you have is based on the characteristics of the cells involved in your disease and their behavior. The type of lymphoma you have helps determine your treatment options.

### Classical Hodgkin lymphoma

Classical Hodgkin lymphoma is the more common type of this disease. People diagnosed with this type have large lymphoma cells called Reed-Sternberg cells in their lymph nodes.

Subtypes of classical Hodgkin lymphoma include:

* Nodular sclerosis Hodgkin lymphoma.
* Mixed cellularity Hodgkin lymphoma.
* Lymphocyte-depleted Hodgkin lymphoma.
* Lymphocyte-rich Hodgkin lymphoma.

### Nodular lymphocyte-predominant Hodgkin lymphoma

This type of Hodgkin lymphoma is much rarer. It involves lymphoma cells sometimes called popcorn cells because of how they look. Usually, it is diagnosed early and may need less intensive treatments than the classical type of Hodgkin lymphoma.

**Risk factors**

Factors that can increase the risk of Hodgkin lymphoma include:

* **Your age.** Hodgkin lymphoma is most often diagnosed in people in their 20s and 30s and those over age 65.
* **A family history of Hodgkin lymphoma.** Having a blood relative with Hodgkin lymphoma increases the risk of Hodgkin lymphoma.
* **Being male.** People who are assigned male at birth are slightly more likely to develop Hodgkin lymphoma than are those who are assigned female at birth.
* **Past Epstein-Barr infection.** People who have had illnesses caused by the Epstein-Barr virus are at higher risk of Hodgkin lymphoma than are those who haven't. One example is infectious mononucleosis.
* **HIV infection.** People who are infected with HIV have an increased risk of Hodgkin lymphoma.

There's no way to prevent Hodgkin lymphoma.

**SYMPTOMS**

Signs and symptoms of Hodgkin lymphoma may include:

* Painless swelling of lymph nodes in the neck, armpits or groin.
* Fever.
* Feeling very tired.
* Night sweats.
* Weight loss that happens without trying.
* Itchy skin.

## Diagnosis and test

Hodgkin lymphoma diagnosis often begins with an exam that checks for swollen lymph nodes in the neck, underarm and groin. Other tests include imaging tests and removing some cells for testing. The type of tests used for diagnosis may depend on the lymphoma's location and your symptoms.

### Physical exam

A healthcare professional may start by asking about your symptoms. The health professional also may ask about your health history.

Next, the healthcare professional may feel and press on parts of your body to check for swelling or pain. To find swollen lymph nodes, the healthcare professional may feel your neck, underarms and groin. Be sure to say if you have felt any lumps or pain.

### Blood tests

A sample of your blood is examined in a lab to understand your health and look for signs of cancer.

### Biopsy

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For Hodgkin lymphoma, the biopsy typically involves removing one or more lymph nodes. The lymph nodes go to a lab for testing to look for cancer cells. Other special tests give more details about the cancer cells. Your healthcare team uses this information to make a treatment plan. Sometimes a biopsy is taken from other parts of the body, such as the liver, to look for signs of Hodgkin lymphoma.

### Imaging tests

Your healthcare team may recommend imaging tests to look for signs of lymphoma in other areas of your body. Tests may include a chest X-ray, CT, MRI and positron emission tomography scans, also called PET scans.

### Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. The cells are sent for testing. Tests can look for Hodgkin lymphoma cells.

### Hodgkin lymphoma stages

Your test results are used to assign a stage to your Hodgkin lymphoma. The stage helps determine the seriousness of your condition and the treatments most likely to help you.

Hodgkin lymphoma staging uses the numbers 1 to 4 to indicate the stage. A lower number means the lymphoma cells only involve one or a few areas of lymph nodes. An early-stage cancer is more likely to be cured. As the lymphoma grows to involve more areas of the body, the stage number goes up. A higher number means the cancer is more advanced.

Hodgkin lymphoma stages also may include the letters A and B. The letter A means that you don't have worrying symptoms of lymphoma. The letter B means that you have some symptoms, such as fever or weight loss.

**Treatment**

Many types of treatments exist for Hodgkin lymphoma. Treatment often starts with chemotherapy. Your healthcare team might check to see how the lymphoma is responding and decide whether you need more treatment. Your options might include radiation therapy, chemotherapy, immunotherapy, targeted therapy and bone marrow transplant, also called stem cell transplant. Sometimes, a combination of treatments is used.

The treatment that's best for you depends on the type of Hodgkin lymphoma that you have. Your healthcare team also might consider the stage of your lymphoma, whether you have any symptoms and your overall health.

### Chemotherapy

Chemotherapy treats cancer with strong medicines. Many chemotherapy medicines exist. Most chemotherapy medicines are given through a vein. Some come in pill form.

Classical Hodgkin lymphoma treatment usually involves a combination of chemotherapy and radiation therapy. Sometimes chemotherapy may be the only treatment needed. More-advanced disease may be treated with a combination of chemotherapy and medicines that attack specific chemicals in cancer cells, known as targeted therapy.

For nodular lymphocyte-predominant Hodgkin lymphoma, chemotherapy may be combined with targeted therapy and radiation therapy.

Side effects of chemotherapy depend on the medicines you're given. Common side effects are nausea and hair loss. Serious long-term complications can occur, such as heart disease, lung damage, fertility problems and other cancers.

### Radiation therapy

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

For Hodgkin lymphoma, radiation can be aimed at affected lymph nodes and the nearby areas where the disease might spread. It's usually used with chemotherapy. Radiation therapy may be the only treatment needed for early-stage nodular lymphocyte-predominant Hodgkin lymphoma.

Radiation therapy side effects include fatigue and a sunburn-like reaction on the skin at the site where the radiation is aimed. Other side effects depend on where the radiation is aimed. Radiation to the neck can cause dry mouth and hurt the thyroid. Radiation to the chest can hurt the heart and lungs.

### Bone marrow transplant

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. A bone marrow transplant may be an option if Hodgkin lymphoma returns or doesn't respond to other treatments.

During a bone marrow transplant, your own blood stem cells are removed, frozen and stored. Next, you receive high-dose chemotherapy and radiation therapy to destroy cancer cells in your body. Finally, the stored stem cells are thawed and put back in your body to help build healthy bone marrow.

There is an increased risk of infection after a transplant.

### Targeted therapy

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in cancer cells. By blocking these chemicals, targeted therapy can cause cancer cells to die. Targeted therapy is often combined with chemotherapy for treating nodular lymphocyte-predominant Hodgkin lymphoma.

For classical Hodgkin lymphoma, targeted therapy might be an option in certain situations.

### Immunotherapy

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

For Hodgkin lymphoma, immunotherapy might be considered in certain situations, such as if the disease doesn't respond to other treatments.

**Alternative medicine**

No alternative medicines have been found to treat Hodgkin lymphoma. But integrative medicine may help you cope with the stress of a cancer diagnosis and the side effects of cancer treatment.

Talk with your healthcare professional about your options, such as:

* Art therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation exercises.
* Spirituality.

### When to see a doctor

Make an appointment with a doctor or other healthcare professional if you have ongoing symptoms that worry you. Hodgkin lymphoma symptoms are like those of many more-common conditions, such as infections. The healthcare professional may check for those causes first.

# Key Statistics for Hodgkin Lymphoma

The American Cancer Society’s estimates for Hodgkin lymphoma in the United States for 2025 are:

* About 8,720 new cases (4,840 in males and 3,880 in females)
* About 1,150 deaths (720 males and 430 females)

Children and adults can develop Hodgkin lymphoma, but it's most common in early adulthood (especially in a person’s 20s). The risk of Hodgkin lymphoma rises again in late adulthood (after age 55). Overall, the average age of people when they are diagnosed is 39.

Hodgkin lymphoma is rare in children younger than 5 years old. But it's the most common cancer diagnosed in adolescents ages 15 to 19 years.

Incidence rates have declined by about 1% each year for Hodgkin lymphoma since the mid-2000s.

Treatments used today cure about 8 out of 10 cases of Hodgkin lymphoma (HL). Still, important research is going on in many university hospitals, medical centers, and other institutions around the world. Scientists are getting closer to finding out what causes the disease and how to better treat it. This is of special interest for hard-to-treat cases, like those that don't respond to current treatments or come back after treatment. Doctors are also looking for ways to limit the long-term side effects linked to HL treatment.

## Imaging tests

PET/CT scans are commonly used to help doctors stage HL and decide how much treatment needs to be given. Doctors are also looking at whether PET/CT scans done during treatment can help decide if more or less treatment is needed.

Researchers are trying to find out if MRI scans might work as well in children and teens with HL. If so, it would mean less radiation exposure and the resulting long-term side effects in young people.

## Treatment

Overall cure rates for HL are high, but long-term side effects of treatment are an important issue. A very active area of research is directed at learning which patients can be treated with gentler therapy and which patients need stronger treatment.

### Radiation

Doctors are looking to see which patients (especially children) might do just as well with lower doses of radiation, or even no radiation . They're also studying if newer forms of radiation therapy, such as intensity-modulated radiation therapy (IMRT) and proton therapy, might be useful for HL. These approaches focus radiation more precisely on tumors, which limits the doses reaching nearby normal tissues.

### Chemotherapy

A related area of research is finding less-toxic treatments that have fewer serious long-term side effects, yet still cure as many patients as possible. Lower doses of chemotherapy (chemo), as well as new chemo drugs and drug combinations are being studied. Many of these drugs are already used to treat other cancers and have shown promise against HL that has come back (relapsed) after other chemo treatments. Studies are in progress to see if these drugs could work better than the ones now in use.

Doctors are also looking for better chemo drugs to use with stem cell transplant. Again, improving outcomes while limiting long-term side effects is the goal.

Another approach is using newer drugs that better target HL cells. Some of these are described below.

### Targeted therapy

Newer drugs that work differently from standard chemo drugs are now being studied. Researchers are learning a lot about the gene changes found in HL cells. This could lead to drugs that target these changes and spare normal cells. These are known as targeted therapy drugs. Many other types of cancer are already treated with targeted therapies.

Some of these targeted drugs are being studied in combinations, in the hope that they might work better when given together. Many are given along with other cancer treatments, like chemo and/or radiation.

### Immunotherapy (including monoclonal antibodies)

Immunotherapy is treatment that helps the body’s immune system find and attack cancer cells. Immunotherapy is helpful against several types of cancer, including Hodgkin lymphoma.

#### Immune checkpoint inhibitors

Immune system cells normally have substances on them that act as checkpoints to keep them from attacking healthy cells in the body. Cancer cells sometimes use these checkpoints to avoid being attacked by the immune system. Today, drugs that block these checkpoints are used to treat HL after other treatments have been tried. Researchers are now studying other ways to use these drugs. For instance, they're looking at whether these drugs might be used as "maintenance therapy" to keep HL from coming back after transplant. They're also testing them as a first treatment for HL. The use of immune checkpoint inhibitors in children and teens, as well as in older people who are too sick to get standard treatment, is also being studied. Several other checkpoint inhibitor drugs are being studied, too.

#### Chimeric antigen receptor (CAR) T-cell therapy

In this treatment, immune cells called T cells are removed from the patient’s blood and altered in the lab so they have receptors called chimeric antigen receptors, or CARs on their surface. These receptors can attach to proteins on the surface of lymphoma cells. The altered T cells are then multiplied in the lab and put back into the patient’s blood. They can then find the lymphoma cells and launch a precise immune attack against them.

This technique has shown encouraging results in early clinical trials against some hard-to-treat Hodgkin lymphomas. Doctors are still improving how they make the T cells and are learning the best ways to use them. CAR T-cell therapy is only available in clinical trials at this time.

#### Monoclonal antibodies

Monoclonal antibodies (mAbs) are man-made versions of immune system proteins. Some can kill cancer cells by themselves. Others have radioactive molecules or cell poisons attached to them, which help kill cancer cells. An advantage of these drugs is that they seem to target lymphoma cells while having fewer side effects than standard chemo drugs. They may be used alone or along with chemo.

Some mAbs, such as brentuximab vedotin (Adcetris) and rituximab (Rituxan), are already being used to treat some cases of HL. Researchers are now studying if these drugs might be useful in other ways. For instance, brentuximab is now being studied to see if it might be helpful earlier in the course of the disease or as part of the treatment used to get ready for a transplant. And studies are now being done to see if rituximab can help treat classic forms of HL as well as the nodular lymphocyte-predominant type. Researchers are also looking for the best way to use mAbs along with standard treatment. Many newer mAbs are now being studied, too.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Hodgkin disease (Hodgkin lymphoma, HL) involves distinguishing it from a variety of infectious, inflammatory, and neoplastic conditions that can mimic its clinical, histological, and laboratory features.

Infectious and Inflammatory Conditions

* Infectious Mononucleosis (Epstein-Barr Virus infection)
  + Presents with fever, lymphadenopathy, fatigue, and sometimes splenomegaly.
  + Lymph node biopsy shows reactive hyperplasia without Reed-Sternberg cells.
* Tuberculosis (TB)
  + Can cause chronic lymphadenopathy, fever, night sweats, weight loss.
  + Granulomas with caseous necrosis on biopsy differentiate from HL.
* Sarcoidosis
  + Noncaseating granulomas in lymph nodes.
  + May have systemic symptoms and lymphadenopathy mimicking HL.
* Brucellosis, Typhoid fever, Malaria
  + Infectious diseases with systemic symptoms and lymphadenopathy.
  + Diagnosis confirmed by serology, blood cultures, and clinical context.
* Autoimmune diseases:
  + Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA)
  + May cause lymphadenopathy and systemic symptoms but lack neoplastic cells.
* Drug hypersensitivity reactions (e.g., DRESS syndrome)
  + Can cause lymphadenopathy, rash, eosinophilia.

Other Neoplastic and Lymphoproliferative Disorders

* Non-Hodgkin Lymphomas (NHL)
  + Includes diffuse large B-cell lymphoma, follicular lymphoma, angioimmunoblastic T-cell lymphoma, and others.
  + Immunophenotyping and histology differentiate from HL.
* Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)
  + A distinct HL subtype with different morphology and immunophenotype.
* Mediastinal Gray Zone Lymphoma
  + Shares features of classic HL and primary mediastinal large B-cell lymphoma; requires immunohistochemical and molecular studies.
* Multicentric Castleman Disease
  + Lymphadenopathy with systemic symptoms; lymph node biopsy shows characteristic features.
* Other malignancies:
  + Metastatic carcinoma, melanoma, sarcoma involving lymph nodes.

REFERENCES

[Hodgkin Disease Research | Hodgkin Lymphoma Studies | American Cancer Society](https://www.cancer.org/cancer/types/hodgkin-lymphoma/about/new-research.html)

[Hodgkin lymphoma (Hodgkin disease) - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hodgkins-lymphoma/diagnosis-treatment/drc-20352650)

[Hodgkin lymphoma (Hodgkin disease) - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hodgkins-lymphoma/symptoms-causes/syc-20352646)

<https://www.ncbi.nlm.nih.gov/books/NBK499969/>

**Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL**

**DEFINITION AND DESCRIPTION**

NLPHL is a rare type of blood cancer. It occurs when lymphocytes, a type of white blood cell in the immune system, behave abnormally. Specifically, NLPHL occurs in B lymphocytes.

There are different types of lymphoma: Hodgkin or non-Hodgkin lymphoma. NLPHL is the Hodgkin type, which means Reed-Sternberg cells are present. These are large cancerous cells found in lymph fluid. The word nodular in NLPHL means the lymphoma grows in the lymph nodes. NLPHL differs from other types of Hodgkin lymphoma due to its unique pathology, which can be examined by doctors under a microscope.

This cancer type is slow-growing and not common. NLPHL accounts for about 5 percent of all Hodgkin lymphoma cases

## causes of NLPHL

NLPHL develops when genetic mutations affect genes within the B lymphocytes.

Researchers are unsure about the exact causes of Hodgkin lymphoma and NLPHL. Some evidence suggests that the Epstein-Barr virus, formally known as human gammaherpesvirus 4, can cause DNA changes to B lymphocytes, which in turn can produce Reed-Sternberg cells.

DNA changes to the genes may play a role in NLPHL, but more research is needed.

## NLPHL risk factors

Hodgkin lymphoma risk factors include age (adults in their 20s or older than 55) and gender (male) In the case of NLPHL specifically 86 percent of 1,937 patients were younger than age 65 and 67 percent were male.

## NLPHL symptoms

Symptoms of nodular lymphocyte-predominant Hodgkin lymphoma may include those listed below.

* Lump in the neck, groin or armpit that doesn’t go away (usually painless)
* Unexplained fatigue
* Excessive nighttime sweating
* Weight loss
* Ongoing high fevers

Fever, night sweats and weight loss are classified as “B symptoms” in Hodgkin lymphoma patients, as these symptoms can also be caused by other health issues. Always check with the care team about any concerns regarding unexpected changes in the body.

#### Hodgkin lymphoma treatment: The care you need is one call away

Your multidisciplinary team will work with you to develop a personalized plan to treat your Hodgkin lymphoma in a way that fits your individual needs and goals.

## NLPHL diagnosis and detection

NLPHL is diagnosed by biopsy, a surgical procedure where all or part of a lymph node is removed and examined under a microscope to look for evidence of cancer cells. The type of biopsy used varies, based on the location of the lymph node, but either local or generalized anesthetic will be used to minimize discomfort.

If cancer is found, the care team may order additional tests to determine the stage, grade and type. These may include:

* Positron emission tomography (PET) scan
* Computed tomography (CT) scan
* Magnetic resonance imaging (MRI) test
* Blood tests

### NLPHL stages

**Early:** Known as stage 1 or 2, this cancer type is generally localized or found in several nearby areas of the body.

**Advanced:** Stage 3 or 4 NLPHL has spread to parts of the body distant from the original cancer.

### NLPHL grades

Lymphomas can be either indolent or aggressive. NLPHL is an indolent lymphoma type, meaning it typically grows slowly.

## NLPHL treatment

The patient's care team will discuss appropriate treatment options with the patient, taking into account the following factors:

* Cancer stage and type
* Personal preferences
* Age and overall health
* Whether or not the patient wants to have children in the future
* Symptoms

For early-stage patients without B symptoms, site radiation therapy is the most common treatment—and it may be the only treatment needed. It’s also called external beam therapy and uses external radiation beams to specifically target the tumor.

If the NLPHL is advanced, chemotherapy is the most common treatment. In some patients, chemotherapy is given and then followed with radiation.

Chemotherapy is a treatment that uses medication to kill cancer cells. A number of different chemotherapy drugs can be used for NLPHL, and sometimes several are combined together.

## Nodular lymphocyte predominant Hodgkin lymphoma survival rate

Because NLPHL is a rare type of lymphoma, survival statistics are based on small case studies. One study of 73 people with nodular lymphocyte predominant Hodgkin lymphoma found that overall 10-year survival was 94 percent, and 10-year progression-free survival was nearly 76 percent.

Keep in mind that the survival rate for NLPHL depends on a variety of factors, including the patient’s age, overall health and the extent of the disease, so the patient should always talk to his or her care team about his or her individual prognosis.

**Epidemiology of Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL):**

* NLPHL is a rare subtype of Hodgkin lymphoma, accounting for approximately 5–10% of all Hodgkin lymphoma cases.
* The annual incidence is estimated at about 0.1 to 0.3 per 100,000 persons (or roughly 1 to 3 cases per million per year) in various populations.
* NLPHL shows a marked male predominance, with a male-to-female ratio of approximately 3:1.
* The median age at diagnosis is typically in the 30 to 40 years range, with disease onset often occurring before age 40 but spanning all ages.
* Compared to classical Hodgkin lymphoma (cHL), NLPHL patients more commonly present with early-stage disease (stage I or II in over 60–80% of cases) and have a more indolent clinical course
* NLPHL predominantly involves peripheral lymph nodes (cervical, axillary, inguinal), with mediastinal involvement being rare.
* B symptoms (fever, night sweats, weight loss) are less frequent in NLPHL compared to cHL
* The prognosis is generally excellent, with 10-year overall survival rates exceeding 90% in early-stage disease.
* Despite the indolent course, NLPHL carries a risk of histologic transformation to aggressive large B-cell lymphoma in a subset of patients (around 6–9% over 10 years

**The differential diagnosis of Nodular Lymphocyte-Predominant Hodgki**n Lymphoma (NLPHL) includes several lymphoid and reactive conditions that can mimic its clinical, histologic, and immunophenotypic features. Accurate differentiation is essential due to differences in prognosis and treatment. Key differential diagnoses are:

Classical Hodgkin Lymphoma (cHL), especially Lymphocyte-Rich Subtype (LRCHL)

* LRCHL can resemble NLPHL but differs by:
  + Presence of Reed-Sternberg (HRS) cells rather than lymphocyte-predominant (LP) “popcorn” cells.
  + Neoplastic cells in LRCHL are typically CD30-positive, CD15-positive, CD20-negative, while NLPHL LP cells are CD20-positive, CD30-negative, CD15-negative.
  + LRCHL often shows mediastinal involvement; NLPHL usually involves peripheral nodes.
  + Differences in follicular dendritic cell (FDC) meshworks and T-cell rosettes.

## T-cell/Histiocyte-Rich Large B-Cell Lymphoma (THRLBCL)

* Shares some morphological overlap with NLPHL, especially NLPHL Fan pattern E (diffuse areas).
* THRLBCL is typically diffuse, not nodular, lacks LP cells, and has fewer small B cells.
* Background T cells in THRLBCL are predominantly cytotoxic phenotype, while NLPHL has more follicular helper T cells and T-cell rosettes around LP cells.
* Immunophenotyping and presence/absence of nodularity help distinguish.

## Follicular Lymphoma (Floral Variant)

* Can mimic NLPHL with nodular architecture and small B-cell background.
* Lacks LP cells and T-cell rosettes seen in NLPHL.
* Usually shows complete effacement of nodal architecture and a background of atypical, nonreactive small B cells.

## Progressive Transformation of Germinal Centers (PTGC)

* A benign/reactive condition characterized by enlarged follicles with expanded mantle zones invading germinal centers.
* Does not have LP cells or T-cell rosettes and lacks lymph node effacement.
* PTGC can coexist with NLPHL in the same lymph node.

## Other Reactive Lymphadenopathies

* Follicular hyperplasia, viral infections (e.g., infectious mononucleosis), and other benign conditions may cause lymph node changes but lack neoplastic LP cells.

REFERENCES

<https://emedicine.medscape.com/article/201886-overview>

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6142570/>

[Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)](https://www.cancercenter.com/cancer-types/hodgkin-lymphoma/types/nodular-lymphocyte-predominant)

**Non-Hodgkin lymphoma**

**Definition and description**

Non-Hodgkin lymphoma is a type of cancer that affects the lymphatic system. The lymphatic system is made up of organs, glands, tubelike vessels and clusters of cells called lymph nodes. It's part of the body's germ-fighting immune system.

Non-Hodgkin lymphoma happens when germ-fighting cells in the lymphatic system grow out of control. The cells can form growths, called tumors, throughout the body.

Non-Hodgkin lymphoma is a broad group of lymphomas. There are many subtypes in this group. Diffuse large B-cell lymphoma and follicular lymphoma are among the most common subtypes. The other broad group of lymphoma is Hodgkin lymphoma.

Advances in diagnosis and treatment of non-Hodgkin lymphoma have helped improve the prognosis for people with this condition.

**CAUSES**

The cause of non-Hodgkin lymphoma often isn't known. This cancer starts when germ-fighting white blood cells called lymphocytes develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do.

DNA gives healthy cells instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. In cancer cells, the DNA changes give other instructions. The DNA changes tell the cancer cells to make more cells quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

In non-Hodgkin lymphoma, the cancer cells often build up in the lymph nodes. They also can build up in other parts of the lymphatic system.

Non-Hodgkin lymphoma can affect the:

* Lymph nodes.
* Lymph vessels.
* Adenoids.
* Tonsils.
* Spleen.
* Thymus.
* Bone marrow.
* Rarely, parts of the body that aren't part of the lymphatic system.

### Non-Hodgkin lymphoma types

Non-Hodgkin lymphoma most often begins in the:

* **B cells.** B cells are a type of lymphocyte that fights infection. B cells make antibodies against foreign invaders. Most non-Hodgkin lymphoma arises from B cells. Subtypes of non-Hodgkin lymphoma that involve B cells include diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt's lymphoma.
* **T cells.** T cells are a type of lymphocyte that kills foreign invaders directly. Non-Hodgkin lymphoma happens much less often in T cells. Subtypes of non-Hodgkin lymphoma that involve T cells include peripheral T-cell lymphoma and cutaneous T-cell lymphoma.

Treatment depends on whether non-Hodgkin lymphoma arises from B cells or T cells.

**Risk factors**

Factors that may raise the risk of non-Hodgkin lymphoma include:

* **Medicines that lower the immune response.** Taking medicines that manage the immune system after an organ transplant might raise the risk of non-Hodgkin lymphoma.
* **Infection with certain viruses and bacteria.** Certain infections seem to raise the risk of non-Hodgkin lymphoma. Viruses linked to this type of cancer include HIV and Epstein-Barr virus. Bacteria linked to non-Hodgkin lymphoma include the stomach ulcer-causing bacterium Helicobacter pylori.
* **Chemicals.** Certain chemicals, such as those used to kill insects and weeds, may raise the risk of non-Hodgkin lymphoma. More research is needed to find the possible link between pesticides and non-Hodgkin lymphoma.
* **Older age.** Non-Hodgkin lymphoma can happen at any age. But it's most common in people 60 or older.

There's no way to prevent non-Hodgkin lymphoma.

**Symptoms**

Signs and symptoms of non-Hodgkin lymphoma may include:

* Swollen lymph nodes in the neck, armpits or groin.
* Belly pain or swelling.
* Chest pain, coughing or trouble breathing.
* Feeling very tired.
* Fever.
* Night sweats.
* Weight loss without trying.

## Diagnosis and test

Non-Hodgkin lymphoma diagnosis often begins with an exam that checks for swollen lymph nodes in the neck, underarms and groin. Tests include imaging tests and removing some cells for testing. The tests used to detect non-Hodgkin lymphoma may depend on the cancer's location and your symptoms.

### Physical exam

A healthcare professional checks for swollen lymph nodes in your neck, underarms and groin. The health professional also checks for a swollen spleen or liver.

### Blood and urine tests

Tests of your blood and urine may help rule out an infection or other disease.

### Imaging tests

Tests to look for lymphoma cells in other parts of the body may include CT, MRI and positron emission tomography, also called PET.

### Lymph node biopsy

Your healthcare professional may suggest a lymph node biopsy to look for cancer cells. A biopsy is a procedure to remove a sample of tissue for testing in a lab. A lymph node biopsy involves removing all or part of a lymph node. In the lab, tests may show whether you have non-Hodgkin lymphoma and, if so, which type.

### Bone marrow tests

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. The cells are sent for testing.

In a bone marrow aspiration, a needle is used to draw a sample of the fluid. In a bone marrow biopsy, a needle is used to collect a small amount of the solid tissue. The samples most often come from the hip bone.

### Lumbar puncture

A lumbar puncture involves removing some of the fluid around the spinal cord. This procedure also is called a spinal tap. A healthcare professional might recommend this test if there's concern that the lymphoma affects the fluid around the spinal cord. A lumbar puncture involves putting a small needle into the spinal canal in the lower back to withdraw the fluid.

**Treatment**

Non-Hodgkin lymphoma treatment often starts with medicines or radiation therapy. Medicines used for this cancer include chemotherapy, immunotherapy and targeted therapy.

The treatments your healthcare team chooses for you depend on your lymphoma. Your healthcare team considers the types of cells involved and how quickly the cancer is growing. Your team also considers your overall health and what you prefer.

If your lymphoma seems to be growing slowly and doesn't cause symptoms, you might not need treatment right away. Instead, you may have checkups every few months. The checkups help your healthcare team watch your condition and see if your cancer is growing.

### Chemotherapy

Chemotherapy treats cancer with strong medicines. There are many chemotherapy medicines. Most chemotherapy medicines are given through a vein. Some come in pill form.

For many types of non-Hodgkin lymphoma, chemotherapy is the first treatment. Sometimes it's combined with targeted therapy.

### Immunotherapy

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

People with certain types of non-Hodgkin lymphoma may have immunotherapy if other treatments haven't helped.

### Targeted therapy

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

For non-Hodgkin lymphoma, targeted therapy may be used alone. But more often, it's combined with chemotherapy. This mix may be your first treatment. It can be your second treatment if your lymphoma comes back.

### CAR-T cell therapy

Chimeric antigen receptor T cell therapy, also called CAR-T cell therapy, trains the immune system cells to fight non-Hodgkin lymphoma. This treatment begins with removing some white blood cells, including T cells, from the blood.

The cells are sent to a lab. In the lab, the cells are treated so that they make special receptors. The receptors help the cells recognize a marker on the surface of the lymphoma cells. Then the cells go back into the body. There they find and destroy the non-Hodgkin lymphoma cells.

CAR-T cell therapy might be an option for certain types of B-cell non-Hodgkin lymphoma. It's typically used when other treatments haven't worked.

### Bone marrow transplant

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. People with non-Hodgkin lymphoma may have a bone marrow transplant if other treatments haven't helped.

### Radiation therapy

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

For certain types of non-Hodgkin lymphoma, radiation therapy may be the only treatment you need. This may be true if your lymphoma is in just one or two spots and grows slowly.

People with non-Hodgkin lymphoma also may need radiation after chemotherapy to kill any lymphoma cells that might remain. Radiation also can relieve symptoms and improve quality of life.

### When to see a doctor

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you.

**Alternative medicine**

No alternative medicines have been found to cure non-Hodgkin lymphoma. But alternative medicine may help you cope with a cancer diagnosis and the side effects of cancer treatment. Talk with your healthcare team about your choices, such as:

* Art therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation exercises.
* Spirituality.

**EPIDEMIOLOGY**

* 7.1 per 100,000 people. The incidence varies geographically, with higher rates generally observed in regions with higher socio-demographic index (SDI).
* Trends:  
  From 1999 to 2021, NHL incidence showed a slow upward trend globally (average annual percentage change ~0.3%), especially in low to middle SDI regions where increases of 3–4% per year have been reported. In contrast, high SDI regions have experienced stable or slightly declining incidence rates. In the United States, incidence rates have declined by about 1% per year since 2015.
* Mortality:  
  Despite rising incidence in some areas, age-standardized mortality rates (ASMR) and disability-adjusted life years (DALYs) have declined globally (AAPC about -0.6% to -0.8% per year), reflecting improvements in treatment and diagnosis. In the US, NHL death rates decreased by about 2% per year from 2013 to 2022.
* Prevalence:  
  The age-standardized prevalence rate (ASPR) of NHL has increased, consistent with improved survival and aging populations[1](https://pubmed.ncbi.nlm.nih.gov/40165194/).
* Demographics:
  + NHL can occur at any age but is more common in older adults, with more than half of cases diagnosed in people aged 65 or older.
  + It is one of the more common cancers in children, teens, and young adults but less frequent than in older populations.
  + Males have a slightly higher incidence than females.
* Regional Variations:
  + Significant increases in NHL incidence have been observed in parts of South America (e.g., Colombia, Chile), Eastern Europe, and Central Asia.
  + Moderate decreases or stable trends have been reported in North America, Western Europe, and some parts of Asia.
  + The burden of NHL is rising more sharply in low and middle SDI regions, highlighting disparities in healthcare access and risk factor prevalence

REFERENCES

[Non-Hodgkin lymphoma - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/non-hodgkins-lymphoma/diagnosis-treatment/drc-20375685)

[Non-Hodgkin lymphoma - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/non-hodgkins-lymphoma/symptoms-causes/syc-20375680)

## Burkitt lymphoma

**Definition and description**

Burkitt lymphoma is a rare, fast-growing cancer of B cells — a type of white blood cell. It’s a form of non-Hodgkin lymphoma that most often affects children and young adults. Other names for this condition include Burkitt’s disease, Burkitt’s lymphoma and Burkitt’s tumor.

It typically starts in lymph nodes in your abdomen or pelvis, but it can also spread to your:

* Belly
* Bone marrow
* Gastrointestinal tract
* Jaw
* Spleen
* Throat
* Tonsils

Because it grows so fast, Burkitt lymphoma can be life-threatening. But with quick treatment, many people go into long-term remission. That means symptoms go away and stay away.

### Types of Burkitt lymphoma

There are three types:

* Endemic: This type is most common in parts of Africa and is linked to Epstein-Barr virus (EBV).
* Sporadic: This type is common in the U.S., especially in kids. It makes up over 40% of childhood non-Hodgkin lymphoma cases.
* Immunodeficiency-related: This affects people with weakened immune systems, like those with HIV/AIDS.

## Symptoms and Causes

Symptoms can appear suddenly and include:

* Belly pain, nausea or vomiting
* Fever, tiredness and night sweats
* Loss of appetite and unintended weight loss
* Swollen lymph nodes

These symptoms can look like common illnesses, but if they get worse, see a healthcare provider. Burkitt tumors can double in size within days.

### Burkitt lymphoma causes

Experts don’t know exactly what causes Burkitt lymphoma. It’s linked to changes (variations) in a gene called *MYC*, which helps control cell growth. A type of genetic glitch, called translocation, can cause this gene to become overactive.

In the U.S., some people who have Epstein-Barr virus (EBV) also have Burkitt lymphoma. But not everyone who has EBV develops Burkitt lymphoma.

#### Complications

Possible complications include:

* Low blood cell counts, needing transfusion of blood products
* Tumor lysis syndrome
* Weakened immunity

Tell your provider if your symptoms become hard to manage.

## Diagnosis and Tests

To diagnose Burkitt lymphoma, your provider may start with a lymph node biopsy. Other tests may include:

* CT scan: Looks for tumors in your chest, belly or pelvis
* PET scan: Highlights areas with cancer
* Bone marrow biopsy: Checks if cancer is in the marrow
* Spinal tap (lumbar puncture): Looks for cancer cells in spinal fluid

#### Stages of Burkitt lymphoma

Healthcare providers use stages to show how far the cancer has spread:

* Stage I (1): One area or lymph node is affected.
* Stage II (2): Cancer is in two or more areas on the same side of your breathing muscle (diaphragm).
* Stage III (3): Cancer is on both sides of your diaphragm.
* Stage IV (4): Cancer has spread outside your lymph system (like to your liver, lungs or bone marrow).

## Management and Treatment

Because Burkitt lymphoma grows fast, treatment needs to start quickly. Options include:

* Chemotherapy: Main treatment, often intense and started right away
* Immunotherapy: Helps your immune system find and attack cancer
* Radiation therapy: Sometimes used with chemo, mostly for adults
* Stem cell transplant: May help if cancer returns after treatment
* Surgery: Used in rare cases, like when a tumor blocks your intestines

### When to see a doctor

Your provider will schedule regular follow-ups to monitor your health. These appointments may include blood tests and CT scans.

Call your provider if you or your child has:

* Chest pain or shortness of breath
* Fever over 100.4 degrees Fahrenheit (38 degrees Celsius)
* Nosebleeds or bleeding gums
* Pain that won’t go away
* Pale skin or easy bruising

## Outlook / Prognosis

Burkitt lymphoma is curable in many cases. It responds well to treatment, especially in kids and teens. Children tend to handle chemotherapy better than adults, who may have other health issues that can make treatment harder.

#### Burkitt lymphoma survival rates

While Burkitt lymphoma is aggressive, many people respond well to treatment. Here’s what the survival rates typically look like:

* Early-stage in kids: Over 90% survive long-term.
* Advanced-stage in kids: 80% to 90% survive.
* Adults: Over 50% go into remission with treatment.

These are only averages. Your outcome may be different, so talk to your provider for more personal details.

#### Self-care tips

Treatment can be tough, but there are ways to cope:

* Find support: Talking to others with similar experiences can help.
* Rest: Give yourself time to recover.
* Eat well: A dietitian can help you stay strong during treatment.
* Plan ahead: Ask your provider what to expect. Let loved ones support you.
* Support your child: A child life specialist can help kids deal with the emotional side of illness.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Burkitt lymphoma primarily includes other CD10 positive B-cell lymphomas: diffuse large B-cell lymphoma (DLBCL), high-grade B cell lymphoma, high-grade follicular lymphoma, and B-cell acute lymphoblastic leukemia/lymphoma (B-ALL). Both DLBCL and high-grade B cell lymphomas typically have larger cells with more pleomorphism than is expected with Burkitt lymphoma. BCL2 positivity and a Ki67 proliferation index <90% favor a diagnosis other than Burkitt lymphoma. Finding an *MYC* translocation is not diagnostic of Burkitt lymphoma; approximately 10% of DLBCL have an MYC translocation. B-ALL may resemble Burkitt lymphoma in size, but it typically has finer chromatin. By immunohistochemistry or flow cytometry, B-ALL will often express markers of immaturity, eg, CD34 and TdT.

Some uncommonly encountered entities should also be considered. Cases with Burkitt lymphoma-type morphology that lack an MYC translocation should be examined for abnormalities of chromosome 11q for the diagnosis of Burkitt-like lymphoma with 11q aberration. The prognosis for this recently described entity appears similar to that of Burkitt lymphoma.

**EPIDEMIOLOGY**

Burkitt lymphoma accounts for approximately 1% to 5% of all non-Hodgkin lymphomas.Burkitt lymphoma is more common in Caucasians than in persons of African or Asian descent. As with most types of lymphoma, Burkitt lymphoma is more prevalent in males, with a 3 to 4:1 male-to-female ratio.

The distribution of endemic cases of Burkitt lymphoma in Africa and Papua New Guinea corresponds to areas where malaria and Epstein-Barr virus are prevalent. In children younger than 18, the incidence is approximately 3 to 6 cases per 100,000 children annually. The average age of diagnosis is 6 years.

The sporadic form is localized to North America and Europe, with a median diagnosis age of 30 years. Sporadic Burkitt lymphoma has an annual estimated incidence of 4 per 1 million children younger than 16 years of age, whereas the incidence is 2.5 per 1 million in adults. The average age of diagnosis in pediatric patients is 3 to 12 years of age.

The immunodeficiency-associated variant has an incidence of 22 per 100,000 person-years in the United State

REFERENCES

[Burkitt Lymphoma - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK538148/#article-18711.s10)

[Burkitt Lymphoma: Symptoms, Causes & Treatment](https://my.clevelandclinic.org/health/diseases/22777-burkitt-lymphoma)

### 

### Diffuse large B-cell lymphoma

**Definition and description**

Diffuse large B-cell lymphoma, or DLBCL, is a blood cancer that involves changes in your B cells, a particular type of white blood cell (lymphocyte). It’s the most common form of aggressive non-Hodgkin lymphoma and a type of B-cell lymphoma.

DLBCL affects your lymphatic system. Your lymphatic system is a network of tissues, vessels and organs that help fight infection in your body. Normal B cells are a part of that infection-fighting network. But with DLBCL, healthy B cells change into fast-growing cancer cells that overtake healthy ones. They’re no longer able to fight off infection-causing invaders, like viruses and bacteria.

With diffuse large B-cell lymphoma, cancerous B cells may appear in your lymph nodes. But they may also appear in virtually any organ, including your gastrointestinal tract, thyroid, skin, breast, bone or brain.

Although it’s aggressive, DLBCL is often treatable and curable — especially with early diagnosis and treatment.

#### Types of DLBCL

The World Health Organization (WHO) has identified over a dozen different types of DLBCL. Each type’s unique traits tell healthcare providers how the cancer will likely progress and respond to treatment. The classifications depend on things like:

* Genetic changes. The genetic changes in the lymphoma cells are the most important identifier.
* The part of your body where DLBCL starts. For example, primary CNS lymphoma starts in your central nervous system (CNS). Primary mediastinal B-cell lymphoma starts in the center of your chest (mediastinum).
* If there’s an association with a virus. Some types of DLBCL happen in people with a specific virus. For example, people with EBV-positive DLBCL have an Epstein-Barr virus infection.

Understanding how the specific type of diffuse large B-cell lymphoma will impact your care journey is important, but the specifics can be confusing. Ask your provider to explain how your type of DLBCL will impact treatment options and outlook.Diffuse large B-cell lymphoma is the most common type of lymphoma. But as cancer diagnoses go, it’s still uncommon overall. According to the National Cancer Institute, in 2020, about 6 people in 100,000 received a DLBCL diagnosis. In comparison, about 500 people in 100,000 received a diagnosis of cancer affecting any part of their bodies.

## Symptoms and Causes

The symptoms most people notice with diffuse large B-cell lymphoma are swollen lymph nodes in their neck, armpits or groin. They usually appear as a lump that doesn’t go away and seems to be getting larger. The lump isn’t usually painful, but it can be.

About 30%of people with DLBCL have “B symptoms,” which include:

* A fever above 103 degrees Fahrenheit (39.5 degrees Celsius) that lasts longer than two days or comes and goes
* Unexplained weight loss that involves losing more than 10% of your body weight over six months
* Heavy night sweats (so intense that it drenches your sheets)

Having these symptoms doesn’t necessarily mean you have diffuse large B-cell lymphoma. That said, you should contact a healthcare provider anytime you notice changes in your body that last for several weeks.

### Causes of diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma happens when B cells mutate (change). These are acquired genetic mutations, meaning you develop them during your lifetime instead of being born with them.

#### Risk factors

Medical researchers aren’t sure what triggers the mutations in DLBCL, but they’ve identified several factors that may increase your risk. Risk factors for diffuse large B-cell lymphoma include:

* Age. Most people diagnosed with DLBCL are in their 60s. The average age of diagnosis is 64 years old.
* Sex. DLBCL is slightly more common in males.
* Race. DLBCL affects more people who are white than people who are Black.
* Family history of DLBCL. The genetic mutations in DLBCL aren’t hereditary, which means, they don’t run in families. Still, studies show you’re at a slightly higher risk if a first-degree biological relative (parent, sibling or child) also has DLBCL. Medical researchers aren’t sure why.
* Infections. Viral infections associated with DLBCL include Epstein-Barr virus, human immunodeficiency virus (HIV) and hepatitis B and C.
* Weakened immune system. Having a condition that impacts your immune system is the most significant risk factor for DLBCL. Examples include having a primary immunodeficiency or autoimmune disorder, or taking immunosuppressants after an organ transplant.
* Increased body mass index (BMI) in young adults. The risk is especially high for young adults with obesity that persists throughout adulthood.
* Exposure to toxic substances. Exposure to pesticides used in farming and certain chemicals used in manufacturing may increase your risk.

## Diagnosis and Tests

Healthcare providers diagnose DLBCL with a lymph node biopsy. This procedure removes all or part of a lymph node to check it for cancer cells. They also do genetic testing to learn which cell mutations are involved.

If you do have DLBCL, your provider may order additional tests to learn more about it, including whether it’s spread beyond your primary lymph node. Tests include:

* Blood tests. These include a complete blood count (CBC) to check your general health and tests that detect viruses, like HIV, EBV and hepatitis B and C.
* Lactate dehydrogenase (LDH) test. This test checks the level of LDH (an enzyme) in your body fluid. Over 50% of people with DLBCL have high levels.
* Imaging tests. You may need a CT scan, MRI or PET scan to show whether the cancer has spread throughout your body.
* Bone marrow biopsy. This test checks for lymphoma cells in your bone marrow.
* Lumbar puncture. This test checks for lymphoma cells in the fluid surrounding your spinal cord.

#### Stages of diffuse large B-cell lymphoma

Healthcare providers use cancer staging systems to determine how advanced the cancer is. This helps them develop treatment plans and estimate prognosis, or expected outcome. The stages of DLBCL are:

* Stage I: The cancer is in one lymph node, one lymph organ (thymus, spleen and tonsils) or in just one area of a single organ outside of your lymph system.
* Stage II: This is when there’s lymphoma in two or more lymph node groupings or lymph node organs on the same side of your diaphragm.
* Stage III: This stage is when there’s cancer in lymph nodes or lymph tissue on both sides of your diaphragm.
* Stage IV: DLBCL has spread to organs outside of your lymph system, like your bone marrow, liver or lungs.

Your provider may refer to stage I and II DLBCL as “early stage” and stage III and IV DLBCL as “advanced stage.”

## Management and Treatment

One of the most common treatments for diffuse large B-cell lymphoma is R-CHOP. It combines the monoclonal antibody drug rituximab with three chemotherapy drugs and a corticosteroid.

This treatment is safe and effective but doesn’t always work or keep DLBCL from coming back (recurring). Studies show relapses or recurrent cancer affect an estimated 30% to 40% of people with DLBCL who receive R-CHOP. If that happens, your provider may recommend the following treatments:

* Second-line therapy and autologous stem cell transplant. Second-line therapy is intensive treatment with combined cancer drugs.
* CAR T-cell therapy. This treatment is a type of immunotherapy that helps your T cells (a type of white blood cell) fight cancer more effectively.
* Targeted therapy. This treatment targets the genetic changes or mutations that cause diffuse large B-cell lymphoma.

## Outlook / Prognosis

While some DLBCL can be life-threatening and difficult to treat, healthcare providers can often cure it using a combination of cancer drugs. Often, front-line or initial treatment sends DLBCL into complete remission. This means there are no signs and symptoms of cancer. Front-line treatment cures about 60% of people with DLBCL. In general, people who are cancer-free two years after their diagnosis can expect to live as long as most people in their age group.

According to the National Cancer Institute, 64.7% of all people with DLBCL are alive five years after diagnosis. Like many kinds of cancer, survival rates increase for people with early-stage cancer.

Still, while cure rates and survival rates may be helpful, your experience depends on many factors, including the type of DLBCL, cancer stage and your overall health. These are factors that only your healthcare provider knows about. Your provider is your best resource for answering questions about what to expect.

## Prevention

There’s no guaranteed way to prevent DLBCL and nothing you can do about risk factors you can’t control, like having an immunodeficiency. But you can take steps to reduce your risk of developing certain infections linked to DLBCL, like hepatitis and HIV. You can also work to maintain a BMI (body mass index) that’s healthy for you.

## Living With

It can be stressful and exhausting to live with any form of cancer, including diffuse large B-cell lymphoma. It’s important that you do what you can to take care of yourself throughout DLBCL treatment. Here are some suggestions:

* Focus on nutrition. Know what foods to eat and avoid, so you’re nourishing your body.
* Rest. Fatigue is the most common side effect of DLBCL treatment. Get as much rest as you can.
* Develop an exercise routine. Gentle exercise may help you cope with stress.
* Find support. Diffuse large B-cell lymphoma is a rare condition. You may feel as if no one understands what you’re going through. Connecting with people who are in your situation may help.

### When should I see a doctor?

You’ll see your healthcare provider throughout your treatment. They’ll monitor your health and check how the treatment is working.

Afterward, you may see your provider every three to four months for the first two years and then less frequently for the next three years. That’s because diffuse large B-cell lymphoma may come back. Contact your healthcare provider if you notice changes in your body that may mean the cancer has recurred.

**Differential Diagnosis**

The differential diagnoses include infectious mononucleosis, Hodgkin lymphoma, T-cell lymphomas, and other large cell malignancies such as carcinomas, melanoma, and Kikuchi disease. Melanomas can also involve the lymph nodes but can be differentiated from DLBCL by positive S100, HMB-45, and Melan A staining.

**EPIDEMIOLOGY**

The incidence of non-Hodgkin lymphoma in the United States is approximately 7 cases per 100,000 per year. DLBCL accounts for about 25% of all NHL cases worldwide. DLBCL is the most common NHL, followed by FL. The disease occurs more frequently in whites, followed by African Americans and Asians with male preponderance and a median age of 64 years. The overall incidence increases exponentially with age.

REFERENCES

[Diffuse Large B-Cell Lymphoma - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK557796/#article-24581.s10)

[Diffuse Large B-Cell Lymphoma (DLBCL)](https://my.clevelandclinic.org/health/diseases/24405-diffuse-large-b-cell-lymphoma)

### 

### 

### Follicular lymphoma

**Definition and description**

Follicular lymphoma is a very slow-growing cancer that may appear in your lymph nodes, your bone marrow and other organs. You can have follicular lymphoma without having symptoms. Healthcare providers consider follicular lymphoma a chronic illness. There are ways to treat follicular lymphoma, but the condition often comes back. Healthcare providers are hopeful newer treatments may mean a cure for follicular lymphoma is on the horizon.

#### How does follicular lymphoma affect my body?

Follicular lymphoma is a subtype of B-cell lymphoma, a form of non-Hodgkin’s lymphoma. Follicular lymphoma symptoms mirror non-Hodgkin lymphoma symptoms, such as swollen lymph nodes, fever and drenching night sweats.

But many people are diagnosed with follicular lymphoma before they develop symptoms. People who’re in good health and don’t have symptoms may not need immediate treatment. Healthcare providers may recommend watchful waiting. In watchful waiting, healthcare providers monitor your overall health and symptoms.

Follicular lymphoma may affect your emotional well-being long before it affects your physical well-being. A recent study showed people with follicular lymphoma and other slow-growing lymphomas struggle with anxiety because they don’t know if they’ll develop symptoms or need to start treatment.

#### Is follicular lymphoma a serious illness?

Yes, follicular lymphoma can be a serious and challenging illness. Here’s why:

* Transformation: Follicular lymphoma can change or transform into diffuse large B-cell lymphoma (DLBCL). This is a more aggressive cancer that typically causes new and more significant symptoms, including spreading cancer into other areas of your body. About 3 % of people who have follicular lymphoma develop DLBCL.
* Relapse: Follicular lymphoma symptoms often subside after treatment and then come back. This cycle of remission-relapse-remission means people who have follicular lymphoma feel as if they’re never able to say they’re “done” with treatment.

## signs and symptoms of follicular lymphoma

General symptoms may include:

* Painless swelling in your neck, armpit or groin caused by enlarged lymph nodes.
* Fever that infection or other illness is causing.
* Weight loss with no known cause, particularly losing 10% or more of your weight within the past six months.
* Sweating and chills. Drenching night sweats and chills that won't go away may be a sign of illness, including follicular lymphoma.
* Fatigue. This is an ongoing sense of feeling so tired that you can’t manage your daily activities.

### causes of follicular lymphoma

Researchers don’t know all of the factors that cause follicular lymphoma. They do know changes in people’s chromosomes cause about 85% of cases. The changes allow unhealthy or cancerous cells to multiply and grow.

## Diagnosis and Tests

Healthcare providers may use several tests to diagnose follicular lymphoma:

* Biopsy: Healthcare providers may take lymph node tissue samples to test for signs of cancer.
* Positron emission tomography (PET) scans: Healthcare providers use this test to observe cancer cell activity and establish a cancer grade.
* Computed tomography (CT) scan: This test helps healthcare providers monitor cancer and evaluate treatment response.

### stages of follicular lymphoma

Healthcare providers establish cancer stages so they know what kind of treatment may be best to treat the cancer. Follicular lymphoma stages range from I to IV:

* Stage I: Cancer is found in one or more lymph nodes. Healthcare providers diagnose about 25% of all follicular lymphoma cases at this stage.
* Stage II: Cancer is found in lymph nodes above or below your diaphragm. Healthcare providers diagnose about 15% of all follicular lymphoma cases at this stage.
* Stage III: Cancer is found in lymph nodes on both sides of your diaphragm. Healthcare providers diagnose about 26% of all follicular lymphoma cases at this stage.
* Stage IV: Cancer has spread outside of the lymph nodes to bone marrow and/other organ systems. Healthcare providers diagnose about 27% of all follicular lymphoma at this stage.

## Management and Treatment

Healthcare providers may use a combination of watchful waiting and therapy to treat follicular lymphoma. Here’s more information about each potential treatment:

* Watchful waiting or active surveillance: If your healthcare provider recommends watchful waiting, you’ll have regular appointments so they can do physical examinations, laboratory tests and imaging tests.
* Radiation therapy: Healthcare providers may use radiation therapy to treat early-stage follicular lymphoma.
* Monoclonal antibody therapy: Healthcare providers use lab-created antibodies designed to find and kill specific cancer cells.
* Chemotherapy: Healthcare providers may use chemotherapy alone or combine chemotherapy with other treatments.
* Targeted therapy: Targeted therapy uses drugs or other substances to attack cancer cells without hurting normal cells.
* Immunotherapy: Immunotherapy stimulates your immune system. Treatments can fuel your body’s production of cancer-fighting cells or help healthy cells identify and attack cancer cells.
* Bone marrow/stem cell transplantation: Healthcare providers may recommend this treatment if follicular lymphoma comes back after chemotherapy.

## Outlook / Prognosis

Follicular lymphoma is a slow-growing condition that’s considered a chronic illness. Studies show about half of all people diagnosed with follicular lymphoma are alive nearly 20 years after diagnosis. About 90% of people are alive five years after diagnosis.

## Prevention of follicular lymphoma

Unfortunately, researchers haven’t identified ways to reduce the risk of developing this condition. If you’re concerned you may be at risk, ask your healthcare provider to review your medical history, including your family medical history.

## Living With

Self-care is an important part of living with cancer. Self-care suggestions include:

* Establish good eating and exercise habits. Ask to speak with a nutritionist for healthy menu ideas.
* Fatigue is a common symptom and treatment side effect. Pay attention to your body and rest when you need to rest, not just when you can.
* You may be living with cancer for a long time. That’s good news of course, but chronic illness may be challenging. Talking to a therapist or finding a support group may help you navigate the challenges.

### When should I see a doctor?

If you’ve been diagnosed with follicular lymphoma, your healthcare provider will set a schedule of follow-up appointments to monitor your condition and/or your treatment. But you should contact your healthcare provider as soon as possible if you notice changes in your body that may be signs of follicular lymphoma symptoms.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of follicular lymphoma (FL) includes a variety of lymphoid neoplasms and reactive conditions that can mimic its clinical, histologic, and immunophenotypic features. Accurate distinction is crucial for prognosis and treatment.

Reactive Follicular Hyperplasia

* Benign lymph node enlargement with preserved architecture.
* Follicles vary in size and shape, with polarization into light and dark zones and abundant tingible body macrophages.
* No monoclonality or t(14;18) translocation.
* Lack of BCL2 expression in germinal centers (usually BCL2-negative).
* No follicular dendritic cell (FDC) meshwork disruption.

## Diffuse Large B-Cell Lymphoma (DLBCL)

* Aggressive lymphoma that may arise de novo or via transformation from FL (especially grade 3 FL with diffuse areas).
* Shows sheets of large cells, loss of follicular pattern.
* Requires different treatment; FL with areas of DLBCL should be treated as DLBCL.

## Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

* Contains “popcorn” or lymphocyte-predominant (LP) cells, positive for CD20 but negative for CD30 and CD15.
* Different clinical behavior and immunophenotype from FL.

## Mantle Cell Lymphoma (MCL)

* Typically expresses cyclin D1 and SOX11, negative for CD10 and BCL6.
* Usually lacks follicular pattern.
* Can be distinguished by immunohistochemistry and genetic studies (t(11;14)).

## Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

* Usually extranodal, with marginal zone B-cell phenotype.
* Negative for CD10 and BCL6, positive for CD20.
* Lacks t(14;18) translocation.

## Lymphoplasmacytic Lymphoma (e.g., Waldenström Macroglobulinemia)

* Characterized by plasmacytoid differentiation and IgM paraprotein.
* Different immunophenotype and clinical presentation.

## Progressive Transformation of Germinal Centers (PTGC)

* Benign condition with enlarged follicles, may mimic FL floral variant.
* No monoclonality or BCL2 rearrangement.

## Castleman Disease (Hyaline Vascular Variant)

* Shows prominent follicular dendritic cells and vascular proliferation.
* Lacks monoclonal B-cell proliferation.

**Epidemiology of Follicular Lymphoma (FL)**:

* Incidence:
  + FL is the second most common subtype of non-Hodgkin lymphoma (NHL) in the United States and Western countries, accounting for about 20–40% of all NHL cases in these regions.
  + The age-standardized incidence rate in high-income countries is approximately 2.4 to 3 per 100,000 persons per year.
  + Some sources report an incidence of about 6 new cases per 100,000 persons per year in the US, reflecting variations in data sources and population.
  + Incidence is generally lower in Eastern Europe, Asia, and developing countries, about threefold less than in Western populations.
* Prevalence and Trends:
  + The prevalence of FL is increasing, partly due to improved survival and aging populations.
  + In the US and Western Europe, the 20-year prevalence of FL has increased by approximately 5% (US) and 12% (Western Europe) between 2020 and 2025.
  + Global data show a rising burden of lymphoma subtypes including FL, especially in low and middle socio-demographic index (SDI) regions, while some high SDI regions show stable or modest declines.
* Demographics:
  + FL primarily affects adults with a median age at diagnosis around 60 years.
  + There is a slight female predominance in some populations, though data vary.
  + The disease is rare in children.
* Geographic Variation:
  + FL is most common in North America and Western Europe.
  + Lower incidence rates are observed in Eastern Europe, Asia, and developing countries.
  + Regional increases in NHL, including FL, have been noted in South America (e.g., Colombia, Chile), parts of Eastern Europe, and Central Asia.
* Risk Factors:
  + Exposure to pesticides and herbicides has been linked to increased FL risk.
  + Aging population and improved diagnostic techniques contribute to rising incidence.
* Mortality:
  + FL is generally an indolent lymphoma with favorable prognosis; death rates are lower compared to aggressive NHL subtypes.
  + Death rate reported as approximately 0.4 per 100,000 persons per year in the US.

References

[Follicular Lymphoma: Stages, Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/22606-follicular-lymphoma)

<https://www.ncbi.nlm.nih.gov/books/NBK538206/>

<https://emedicine.medscape.com/article/203268-overview>

<https://www.ncbi.nlm.nih.gov/books/NBK538206/>

## Mantle Cell Lymphoma

**Definition and description**

Mantle cell lymphoma (MCL) is a rare blood cancer that starts in your lymphocytes (a type of white blood cell). It’s a subtype of non-Hodgkin lymphoma.

In most cases, MCL begins as a slow-growing cancer that later grows rapidly. It spreads throughout your lymphatic system. In its advanced stages, the cancer spreads from your lymph nodes to other areas, like your bloodstream, bone marrow and digestive system.

With mantle cell lymphoma, you might have periods of remission followed by periods of recurrence. That means the cancer can go away and come back, often several times. Treatment can’t cure MCL, but it can lengthen the amount of time you’re in remission.

Mantle cell lymphoma is rare, affecting about 1 in 200,000 people. Anyone can develop this type of cancer. People between the ages of 60 and 70 have a slightly higher risk.

### Types of mantle cell lymphoma

The two types of mantle cell lymphoma are:

* Classical MCL. This type starts in your lymph nodes but usually spreads to other areas of your body. It’s usually more aggressive (fast-growing). Most MCL cases are the classical type.
* Leukaemic non-nodal MCL. This type usually causes a swollen spleen and lymphoma cells in your blood and bone marrow. It tends to grow more slowly than the classical type.

## Symptoms and Causes

MCL symptoms vary from person to person and can look like ordinary illnesses. They may not always appear to be cancer-related. That’s one reason why mantle cell lymphoma is usually in the later stages at the time of diagnosis.

You might not have any symptoms with MCL. But if you do, they might include:

* Bruising
* Headaches
* Fatigue
* Fever
* Indigestion
* Loss of appetite
* Night sweats
* Swollen lymph nodes
* Weakness
* Unexplained weight loss

### Causes of mantle cell lymphoma

Most of the time, mantle cell lymphoma happens when certain genes mutate (or change) and alter how your B cells function. Researchers don’t know what triggers this genetic change, but here’s how it works:

1. Abnormal B cells make too much cyclin D1 (a protein that helps B cells grow).
2. The cyclin D1 overload makes B cells duplicate and multiply uncontrollably.
3. The duplicate cells make tumors.

### complications of mantle cell lymphoma

As mantle cell lymphoma progresses, you might develop complications like:

* Gastrointestinal bleeding
* Ruptured spleen
* Tumor lysis syndrome

## Diagnosis and Tests

Your healthcare provider may use many different tests to diagnose MCL, including:

* Lab tests. These may include a complete blood count (CBC), comprehensive metabolic panel (CMP), LDH test or a uric acid level test.
* Biopsies. Your healthcare provider may also recommend a lymph node biopsy or bone marrow biopsy. These procedures can help confirm the presence of cancer cells. Once a provider takes a tissue sample, they’ll send it to a pathologist for testing.
* Imaging tests. Your provider might take imaging tests to determine how far the cancer has spread. Depending on the location of the cancer, you might need a colonoscopy, CT scan, EGD (esophagogastroduodenoscopy) or PET scan.

Healthcare providers usually suspect mantle cell lymphoma after routine blood work shows a high lymphocyte count. If your lab results are abnormal, a healthcare provider will do an exam and ask you to describe your symptoms. They might gently press around your lymph nodes to see if they’re swollen.

### stages of mantle cell lymphoma

Healthcare providers use a disease-specific staging system called the Mantle Cell Lymphoma International Prognostic Index (MIPI). It helps them predict survival rates. In general, late-stage MCL is more likely to come back than early-stage MCL.

Healthcare providers determine cancer stage by finding out how far the cancer has spread:

* Stage I. Localized to one lymph node or cluster of lymph nodes in the same area.
* Stage II. Cancer is in two or more lymph nodes or lymph node clusters on the same side of your diaphragm.
* Stage III. MCL has spread to both sides of your diaphragm. Or it’s in the lymph nodes in your spleen and above your diaphragm.
* Stage IV. Mantle cell lymphoma has spread to distant areas of your body or parts that aren’t lymph nodes.

## Management and Treatment

MCL treatment is different for everyone. The option that’s right for you depends on factors like tumor location and growth.

Treatments for mantle cell lymphoma include:

* Chemotherapy
* Immunotherapy
* Radiation therapy
* Targeted therapy
* Stem cell transplant

You might qualify for some treatments but not others.

If you have MCL, you may want to consider a clinical trial. Clinical trials test new ways to treat cancer. The new treatments might not cure mantle cell lymphoma, but they may give you more symptom-free time to enjoy life. Ask your healthcare provider if you could be a candidate.

## Outlook / Prognosi

Mantle cell lymphoma isn’t a curable lymphoma. But there are treatments that can send it into remission.

Cancer in remission isn’t the same as cancer that’s been cured. Mantle cell lymphoma can come back (relapse) after being in remission for months or years.

The amount of time you experience remission may be shorter with MCL. But newer targeted treatments can increase the remission period. To learn more about your mantle cell lymphoma prognosis, ask your healthcare provider.

#### Survival rate

The five-year survival rate for mantle cell lymphoma is about 50%. That means around half of the people diagnosed with this disease are still alive five years after diagnosis.

Survival rates are just estimates. They can’t tell you how long you’ll live or how you’ll respond to a particular treatment. To learn what survival rates mean for you, talk to your healthcare provider.

## Prevention

You can’t prevent MCL. If you receive a diagnosis, it doesn’t mean you’ve done something wrong. Researchers are learning more about why genes mutate or change within our bodies to create cancers like MCL.

## Living With

Taking care of yourself — physically, emotionally and mentally — is essential with mantle cell lymphoma.

Here are some suggestions that might help:

* Acknowledge your emotions. Ignoring negative feelings won’t make them go away. Honoring your emotions is the first step in finding the support you need.
* Get support. Joining a support group is a great way to find others who are going through similar situations. Ask your healthcare provider about local or online resources.
* Manage your stress. Find ways to relax and bring intention into your daily life. Try meditation or other mindfulness exercises.
* Stick to a routine. The cycle of remission and relapse can make you feel out of sorts. Finding a daily routine and sticking to it can help you regain control.
* Talk to a counselor. It’s important to take care of your mental health. A counselor or therapist can help you sort through complicated emotions.

### When should I see my healthcare provider?

If you’re receiving treatment for mantle cell lymphoma, you’ll see your healthcare provider regularly. They’ll monitor your progress and help you manage side effects.

If your condition is in remission, you’ll have occasional follow-ups. Ask your provider how frequently to schedule these appointments.

**Epidemiology of Mantle Cell Lymphoma (MCL)**:

Incidence:

* + MCL is a relatively uncommon subtype of non-Hodgkin lymphoma (NHL), comprising approximately 3–10% of all NHL cases.
  + The annual incidence is estimated at about 0.5 to 1 case per 100,000 population globally, with slight regional variations.
  + SEER data from the United States indicate an increase in incidence from 0.711 per 100,000 (2000–2006) to 0.800 per 100,000 (2007–2013), largely driven by cases in patients aged 65 years and older.
  + Recent trends (2015–2019) suggest a slight decline in incidence (~0.49% annual decrease), following an earlier period of increase.
* Demographics:
  + MCL predominantly affects older adults, with a median age at diagnosis around 68 years.
  + Most cases occur in patients aged 65–74 years.
  + There is a male predominance, with a male-to-female ratio of approximately 1.46:1.
  + Whites have a higher risk compared to Blacks, Hispanics, and Asian Americans.
* Survival Trends:
  + Relative 5-year survival rates have modestly improved over time, particularly in patients aged 50–64 years (from 61.3% to 67.4%) and those with advanced (stage IV) disease (from 48.0% to 55.1%).
  + Despite improvements, MCL remains an aggressive lymphoma with poorer prognosis compared to many other NHL subtypes.
* Geographic and Global Trends:
  + Exact global prevalence is difficult to determine due to variability in diagnostic criteria and reporting.
  + Incidence and burden of NHL, including MCL, are rising in some regions such as South America (Chile, Colombia), parts of Eastern Europe, and Central Asia.
  + Conversely, some high-income regions (North America, Western Europe, parts of Asia) have stable or slightly declining incidence rates.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis primarily includes SLL/CLL and DLBCL. Both SLL/CLL and mantle cell lymphoma are CD5-positive, mature B-cell lymphomas and may be difficult to distinguish by flow cytometry alone. When there is positivity for CD200 and CD23, the diagnosis is most likely SLL/CLL. Mantle cell lymphoma is typically negative for CD23; it is positive for FMC7. Confirmation of MCL is typically performed by either FISH for t(11;14) or immunohistochemistry for cyclin D1 and/or SOX11. In tissue, uniform positive immunohistochemical expression of B-cells by Cyclin D1 and SOX 11 supports MCL. Focal positivity for Cyclin D1 may be seen in the proliferation centers of SLL/CLL and should not prompt a diagnosis of MCL. Diffuse large B-cell lymphoma is entertained when large cell proliferation is negative for Cyclin D1 and SOX11.

When the architecture of a lymph node is intact and only shows focal involvement by atypical cyclin D1 positive cells, mantle cell neoplasia in situ may be a diagnostic consideration.

References

[Mantle Cell Lymphoma: Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/24030-mantle-cell-lymphoma)

<https://www.ncbi.nlm.nih.gov/books/NBK536985/>

<https://emedicine.medscape.com/article/203085-overview>

### 

### Marginal zone lymphoma

**Definition and description**

Marginal zone lymphoma (MZL) refers to a group of rare, slow-growing non-Hodgkin lymphomas. They typically develop in lymphoid tissue. This tissue contains B cells, a type of white blood cell that’s in parts of your immune system like your lymph nodes and spleen.

Your lymph nodes contain lymphoid follicles. Lymphoid follicles have two zones, or sections — mantle zones and marginal zones. Marginal zones wrap around mantle zones. Marginal zone lymphoma happens when B cells in the marginal zone mutate (change), becoming abnormal cells that multiply excessively.

Marginal zone lymphomas usually affect people aged 60 and older. They tend to be more common in men than in women.

#### What are marginal cell lymphoma types?

There are three types of marginal zone lymphomas:

* Mucosa-assisted lymphoid tissue (MALT) lymphoma: This is the most common type of MZL. Healthcare providers may use the term “extranodal marginal cell lymphoma.” This type of marginal zone lymphoma may develop in the lining of your belly (gastric MALT) or in your lungs, skin, thyroid, salivary gland, bowels or near your eye (non-gastric MALT).
* Nodal marginal zone lymphoma: This type affects your lymph nodes but can appear in your bone marrow.
* Splenic marginal zone lymphoma: This rare type of marginal zone lymphoma affects your spleen, blood and bone marrow.

## Symptoms and Causes

Marginal zone lymphoma typically grows very slowly. You may have this condition without having symptoms. Symptoms vary depending on the condition type. In general, marginal zone lymphomas cause the following symptoms:

* Fever.
* Night sweats.
* Unexplained weight loss.

#### MALT lymphoma symptoms

Extranodal marginal zone lymphoma symptoms vary based on the lymphoma location. For example, MALT lymphoma in your belly may cause:

* Nausea and vomiting.
* Belly pain.
* Feeling full even when you haven’t eaten.

Non-gastric MALT symptoms may include changes in your eye’s surface (conjunctiva) or tear (lacrimal) glands.

#### Nodal marginal zone lymphoma symptoms

Nodal marginal zone lymphoma symptoms may include:

* Fever.
* Night sweats.
* Unexplained weight loss.

#### Splenic marginal zone lymphoma symptoms

Splenic marginal zone lymphoma symptoms may include:

* Fatigue.
* Enlarged spleen.
* Night sweats.
* Unexplained weight loss.

### Causes of marginal zone lymphoma

In general, people with marginal zone lymphoma have a family history of lymphoma, frequent infections or autoimmune diseases. The subtypes have specific causes:

* MALT lymphoma causes include bacterial infections, specifically *H. pylori* infections, autoimmune diseases like Hashimoto’s disease or Sjӧgren’s syndrome, or having a family history of lymphoma.
* Splenic marginal zone lymphoma is linked to hepatitis C and autoimmune diseases.
* Nodal marginal zone lymphoma is associated with hepatitis C.

#### marginal zone lymphoma risk factors

Risk factors include having a family history of lymphoma and having certain infections and autoimmune disorders.

## Diagnosis and Tests

Healthcare providers diagnose the condition by asking questions about your symptoms, your medical history and your family medical history.

#### What tests do providers use to diagnose marginal zone lymphoma?

Tests vary based on the sub-type. In general, tests may include:

* CBC.
* LDH test.
* Beta-2 microglobulin, a tumor marker for blood cancers.
* Liver function tests.
* Renal (kidney) function tests.
* Serum protein immunofixation (IFX). This test checks for changes in your blood.
* Certain bacterial and viral infections like *H. pylori*, hepatitis C and hepatitis.
* CT scan.
* Needle biopsy.
* Bone marrow biopsy.
* Biopsy to obtain samples of cells or tissue from various parts of your body.

#### MZL stages

Healthcare providers use cancer staging systems to plan treatment and develop prognoses. MZL stages are:

* Stage I: Cancer in one lymphatic area.
* Stage II: Cancer in two more lymph nodes located above or below your diaphragm.
* Stage II: Cancer in several lymph nodes above and below your diaphragm.
* Stage IV: Cancer that has spread to multiple organs.

## Management and Treatment

Marginal zone lymphoma grows very slowly. People with this condition may not need immediate treatment. Healthcare providers instead may monitor people’s health until they determine that treatment is necessary. This is “watchful waiting” or active surveillance.

Treatments for MZL vary depending on the subtype but may include:

* Antibiotics to treat bacterial infections, specifically *H. pylori*.
* Chemotherapy.
* Radiation therapy.

## Outlook / Prognosis

That depends on the condition type. For example, antibiotic treatment that eliminates *H. pylori* may cure extranodal marginal zone lymphoma. Other treatments put the condition into remission. Remission happens when cancer treatment eliminates symptoms and tests show no signs of disease. But marginal zone lymphoma may recur (come back) after treatment.

#### What is the survival rate for marginal zone lymphoma?

Survival rates vary based on the type of marginal zone lymphoma. One study suggests the following:

* An estimated 88% of people with extranodal marginal zone lymphoma were alive five years after diagnosis.
* An estimated 79% of people with splenic marginal zone lymphoma were alive five years after diagnosis.
* An estimated 76.5% of people with nodal marginal zone lymphoma were alive five years after diagnosis.

When you think about survival rates, it’s important to remember these are estimates based on other people’s experiences and data collected over time. Your experience may be different.

Marginal zone lymphoma affects people aged 60 and older. In many cases, people with this condition ultimately die from causes other than marginal zone lymphoma.

If you have marginal zone lymphoma, your healthcare provider is your best resource for information about your prognosis.

## Prevention

This condition happens for several reasons, including autoimmune diseases and genetic issues you can’t control.

## Living With

If you’ve been diagnosed with marginal zone lymphoma, contact your provider if:

* You notice changes in your body that may be marginal zone lymphoma symptoms.
* You’re getting treatment and your symptoms get worse.
* You’re in remission, and notice changes that could indicate your condition is coming back (recurring).

#### What can I do to take care of myself?

Self-care is an important part of living with lymphoma, including rare lymphomas such as marginal zone lymphoma. Here are some steps you can take:

* Manage your stress. If you have marginal zone lymphoma, you may not have symptoms that require treatment. While that’s good news, it can be stressful wondering if you’ll have symptoms. Exercise, listening to music or activities like yoga may help.
* Drink enough fluids. Cancer treatment and side effects may cause dehydration.
* Eat a well-balanced diet. Focus on small meals that include fruit, vegetables, nuts and full-fat dairy products.

## Incidence and epidemiology

MZLs represent approximately 5%–15% of all non-Hodgkin lymphomas in the Western world. EMZLs comprise approximately two-thirds and can arise at any extranodal site, usually in the context of chronic antigenic stimulation due either to infections or autoimmune disorders. The stomach is the most common site, followed by ocular adnexa, lung and salivary glands. SMZL accounts for 20% and NMZL for <10% of cases. Aetiological heterogeneity is apparent across the anatomical sites, probably influenced by either intrinsic genetic/molecular characteristics or geographical factors and environmental exposures. Overall, the incidence appears to have increased in the last two decades (possibly because of improved pathological diagnosis), despite a decline in the incidence of *Helicobacter pylori*-associated gastric MZLs.

**Differential Diagnosis of Marginal Zone Lymphoma (MZL)**

Marginal zone lymphoma (MZL) comprises three main subtypes—splenic (SMZL), nodal (NMZL), and extranodal (MALT lymphoma)—each with overlapping but distinct clinical, morphological, immunophenotypic, and molecular features.

Splenic Marginal Zone Lymphoma (SMZL)

* Differential diagnoses:
  + Splenic red pulp diffuses small B-cell lymphoma (SRPL): Overlaps clinically and morphologically with SMZL; both present with splenomegaly and bone marrow involvement.
  + Lymphoplasmacytic lymphoma (LPL): Presence of monoclonal IgM paraprotein, bone marrow involvement, and MYD88 mutation (common in LPL, rare in SMZL).
  + Follicular lymphoma (FL): May involve spleen; distinguished by t(14;18) translocation and CD10/BCL6 positivity.
* Diagnostic tools: Peripheral blood and bone marrow examination, IHC markers (MNDA, IRTA1, T-Bet), and molecular markers (NOTCH2, KLF2 mutations).

Nodal Marginal Zone Lymphoma (NMZL)

* Differential diagnoses:
  + Extranodal MZL (EMZL): Occasionally involves lymph nodes; clinical and radiologic correlation needed.
  + SMZL: Must exclude splenic involvement to confirm NMZL.
  + LPL: Partial lymph node architecture preservation, plasmacytoid cells, Dutcher bodies, and MYD88 mutation.
  + Follicular lymphoma with marginal zone differentiation: FL cells are CD10+, BCL6+, and BCL2+, whereas NMZL cells are usually negative for CD10/BCL6 but positive for MNDA and IRTA1.
  + Small lymphocytic lymphoma (SLL): Different immunophenotype (CD5+, CD23+).
  + Reactive marginal zone hyperplasia: Polyclonal expansion, no clonal B-cell population.
* Diagnostic approach: Morphology, IHC panel (CD20, CD10, BCL6, MNDA, IRTA1), molecular studies (PTPRD mutations in NMZL), and clinical correlation.

Extranodal Marginal Zone Lymphoma (MALT lymphoma)

* Differential diagnoses:
  + Reactive lymphoid hyperplasia or pseudolymphoma: Polyclonal, lacks clonal rearrangements.
  + Other low-grade B-cell lymphomas: Such as follicular lymphoma or lymphoplasmacytic lymphoma depending on site and features.
  + Chronic inflammatory or infectious conditions: May mimic MALT lymphoma histologically.
* Diagnosis: Requires biopsy with IHC (CD20+, CD5−, CD10−), molecular studies, and clinical context (e.g., association with *Helicobacter pylori* in gastric MALT lymphoma).

Cutaneous Marginal Zone Lymphoma (CMZL)

* Differential diagnoses:
  + Cutaneous pseudolymphoma, arthropod bites, urticaria, leukemia cutis, basal cell carcinoma: Clinical and histologic correlation essential.
* Diagnosis: Skin biopsy showing dermal infiltration of small to medium B cells, IHC positive for CD20, CD79a, BCL-2, negative for CD10 and BCL-6.

REFERENCES

[Marginal Zone Lymphomas (MZL): Symptoms and Treatment](https://my.clevelandclinic.org/health/diseases/24915-marginal-zone-lymphoma)

[Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up✰ - Annals of Oncology](https://www.annalsofoncology.org/article/S0923-7534(19)35465-1/fulltext)

### 

### 

### peripheral T-cell lymphoma (PTCL)

**Definition and description**

Peripheral T-cell lymphoma (PTCL) isn’t a single disease. The term refers to a group of aggressive (fast growing) blood cancers that affect your lymphatic system and may spread (metastasize) to other areas of your body. Peripheral T-cell lymphomas are a form of non-Hodgkin lymphoma. They can affect nearly every part of your body and cause many different symptoms. Healthcare providers can successfully treat most subtypes, but the conditions often come back (recur). Medical researchers are studying potential treatments that may help people to live longer with PTCL.

#### Are peripheral T-cell lymphomas common?

No, they aren’t. One global study concluded PTCLs effect 2 in 100,000 people worldwide, and they make up about 10% of cases of non-Hodgkin lymphoma. The lymphomas are more common in Asia, Africa and the Caribbean than in the United States. They typically affect people ages 60 and older, but children and young adults may develop certain types of these lymphomas.

**types of peripheral T-cell lymphoma**

The World Health Organization (WHO) recognizes more than 20 PTCL subtypes. Nearly all PTCL subtypes have distinct genetic markers and other characteristics. According to one global study, the most common PTCL subtypes are:

* **Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS**):This is the most common subtype. PTCL isn’t a specifically defined subtype. Instead, it’s a group of conditions that represent cases that don’t fit well into one of the more specifically defined subtypes. Approximately 30% of all peripheral T-cell lymphoma cases are PTCL-NOS. This subtype affects your lymph nodes, bone marrow, spleen or liver.
* **Angioimmunoblastic T-cell lymphoma (AITL)**: This subtype represents between 15% and 30% of PTCL cases worldwide. It affects your lymph nodes, bone marrow, spleen or liver.
* **Anaplastic large cell lymphoma (ALCL)**: There are different forms of ALCL. They include primary cutaneous ALCL, which affects your skin. Another type, systemic ALCL, affects your lymph nodes, skin and other organs. Some cases of systemic ALCL are further categorized by changes in a specific gene, called anaplastic lymphoma kinase (ALK). ALCL represents approximately 15% of PTCLs.
* **Extranodal natural killer/T-cell lymphoma, nasal type**: This PTCL subtype commonly grows in the tissues of your nose, sinus cavities and upper throat, but it may also spread to your skin, digestive tract and other organs. Approximately 10% of PTCLs are this subtype.
* Intestinal T-cell lymphomas, which account for about 6% of PTCLs. This subtype affects your digestive system and includes enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).
* Adult T-cell lymphoma/leukemia, which may affect your skin and bones. There are four subtypes of ATLL: acute, lymphoma, chronic and smoldering. Acute and lymphoma subtypes are aggressive (fast growing) forms of ATLL. Chronic and smoldering are less aggressive. Each ATLL subtype affects different areas of your body.

## Symptoms and Causes

While each PTCL subtype has specific symptoms, some common symptoms include:

* Swollen lymph nodes: You may have painless swelling in your neck, armpits or groin.
* Unexplained weight loss: This is losing body weight without trying. Losing 10% of your total body weight over six months is a sign of unexplained weight loss.
* Belly (abdominal) pain or swelling: This may happen if your spleen becomes enlarged.
* Persistent fatigue: This is feeling much more tired than usual for at least several days and for no apparent reason.
* Unexplained fever: Often, fevers are signs your body is fighting an infection. A fever that stays above 103 degrees Fahrenheit (39.5 degrees Celsius) for two or more hours after home treatment or lasts longer than two days may be a sign of a serious problem.

Specific subtypes may have other symptoms.

#### Peripheral T-cell lymphoma, not otherwise specified

Symptoms other than ones common to PTCL include:

* Anemia (low red blood cell levels).
* Thrombocytopenia (low platelet levels).
* Itchy red patches on your skin.
* Chest pain or shortness of breath (dyspnea) if there’s cancer in your chest.

#### Angioimmunoblastic T-cell lymphoma

Symptoms other than ones common to PTCL include:

* Night sweats.
* Skin rash.
* Autoimmune disorders like autoimmune hemolytic anemia.

#### Anaplastic large cell lymphoma

Primary cutaneous ALCL

Symptoms include:

* Abnormal reddish or reddish-brown growths on your skin that grow over time.
* Large, raised bumps that itch.
* Growths that become wounds and scab over.

Systemic ALCL

Systemic ALCL causes common PTCL symptoms.

#### Extranodal natural killer/T-cell lymphoma, nasal type

Symptoms include:

* Congestion (your nose feels blocked up).
* Nosebleeds.
* Crust in your nose.
* Painful swelling that affects your face.
* Eye issues like “weepy” eyes or eye pain.

#### Adult T-cell lymphoma/leukemia

The four ATLL subtypes have common PTCL symptoms.

### causes of peripheral T-cell lymphomas

Peripheral T-cell lymphomas happen when your T cells mutate and become cancerous cells. T cells are white blood cells that help defend your body from intruders like germs. When T cells mutate, they turn into cancerous cells that multiply uncontrollably. As they multiply, they build up in your lymph nodes, spleen, liver and other organs and create cancerous tumors.

Experts don’t know exactly what makes T cells mutate to cause peripheral T-cell lymphoma. But research links them to certain medical conditions. For example, one global study showed having celiac disease may increase your risk of developing several types of PTCL, including anaplastic large cell lymphoma. For another example, being infected with Epstein-Barr virus may increase your risk of developing extranodal natural killer/T-cell lymphoma. Having the human T-cell lymphotropic virus Type 1 (HTLV-1) may increase your risk of acute T-cell lymphoma/leukemia.

## Diagnosis and Tests

Healthcare providers may need to do several different tests to find the specific PTCL that’s causing health issues. You may need blood tests, imaging tests, biopsies and genetic tests when pathologists study cancerous cells’ genetic makeup.

#### Blood tests

Providers may test your blood for viruses linked to peripheral T-cell lymphomas. Blood tests may include:

* Complete blood count (CBC).
* Comprehensive metabolic panel (CMP).
* Lactate dehydrogenase (LDH) test.
* Hepatitis B and Hepatitis C tests.
* Human immunodeficiency virus (HIV) test.
* Human T-cell lymphotropic virus Type 1 (HTLV-Type 1) tests.

#### Imaging tests

Imaging tests give healthcare providers information about what’s going on inside your body, including tumors.

* Computed tomography (CT) scan.
* Positron emission tomography (PET) scan.
* Magnetic resonance imaging (MRI) scan.

#### Biopsies

* Lymph node biopsy.
* Skin biopsy.
* Bone marrow biopsy.

### stages of peripheral T-cell lymphoma

Providers use cancer staging systems to develop treatment plans and prognoses, or what you may expect from treatment. They set cancer stages based on factors like PTCL type and where the cancerous T cells are growing. Peripheral T-cell lymphoma stages are:

* Stage I: Cancerous T cells in one lymph node or in one cluster of lymph nodes.
* Stage II: Cancer affects two or more clusters of lymph nodes in the same area of your body.
* Stage III: Cancer affects lymph nodes in both the upper and lower parts of your body.
* Stage IV: Cancer affects lymph nodes and other organs like your lungs or your digestive tract.

## Management and Treatment

There’s no single treatment for the many PTCL subtypes, and treatment may vary depending on cancer stage. Common treatments may include:

* Chemotherapy, combining different types of chemotherapy drugs.
* Radiation therapy, which providers may use along with chemotherapy.
* Targeted therapy, which targets specific genetic changes or mutations that turn healthy cells into cancerous cells.
* Chemotherapy and allogeneic stem cell transplantation to treat PTCL that doesn’t respond to chemotherapy and radiation therapy or that come back after treatment.

You may want to consider taking part in a clinical trial evaluating PTCL treatments.

#### common treatment side effects

Most cancer treatments may cause side effects. For example, chemotherapy and radiation therapy side effects may include:

* Fatigue.
* Chemotherapy brain fog.
* Nausea and vomiting.

## Outlook / Prognosis

That depends on the type and stage of PTCL and whether treatment has put cancer into remission. Remission means you don’t have symptoms and tests don’t find signs of cancer. In some situations, standard treatment can cure PTCL. However, most peripheral T-cell lymphomas come back, which means you’ll need additional treatment or a different kind of treatment.

It’s understandable that you want to know what you may expect from treatment. Consider your healthcare provider your best resource for information about your situation.

## Prevention

No, they can’t. These lymphomas happen when T cells mutate and become cancerous cells. There’s nothing you can do to prevent that.

## Living With

Peripheral T-cell lymphomas are rare, fast-growing cancers. If you have a form of PTCL, here are some suggestions that may help you live with the condition:

* Consider palliative care: This care can help you manage symptoms and treatment side effects. More than that, your palliative care team can support you as you deal with the emotional challenge of living with a serious illness.
* Find support: PTCLs are rare cancers. You may feel as if you’re the only person who knows what you’re going through. You don’t have to face cancer alone. Talk to your healthcare team about support groups so you can connect with others in your situation.
* Take time for self-care: Cancer is stressful. Self-care is an important part of living with PTCL. Talk to your healthcare team about ways to manage stress and how to develop a nutritious diet to keep you strong through treatment.

**EPIDEMIOLOGY**

Experts have found that the overall incidence and frequency of these subtypes varies geographically. PTCL, in general, is more common in Asia and the Caribbean. The most common subtype is called PTCL-not-otherwise specified (PTCL-NOS) and is most frequently diagnosed in individuals living in North America and Europe. Anaplastic large cell lymphoma (ALCL) is common in North America and Europe, whereas angioimmunoblastic T-cell lymphoma (AITL), the second most common subtype, is found more often in Europe. The types known as NK-/ T-cell lymphoma (NKTCL) and adult T-cell leukemia (ATLL) are most common in Asia.

Most PTCL subtypes are aggressive (fast-growing) lymphomas, including PTCL-NOS, AITL, ALCL, enteropathy-type T-cell lymphoma, and extranodal natural killer (NK) cell/T-cell lymphoma.

TCL was thought to occur more frequently in Asia. Rüdiger et al. reported frequencies of PTCL in Vancouver to be 1.6% of all NHL compared to 18.3% in Hong Kong . The international PTCL and NKL project reported PTCL and NKL rates of 5–10% in Western countries compared to 10–20% in Asian countries

In the study, it was also interesting that the incidence of ALCL (both ALK+ and ALK−) in North America (24%) was almost four-times higher than in Asia (6%). Data from Au et al. and our own institution's suggest that the rate of PTCL in the East may actually be similar to the West. The perceived higher rates of PTCL in the East could perhaps be due to the higher incidence of NKL in the East and the differences in diagnostic evaluation. In their institution, they evaluated 148 consecutive cases of TCL and NKL and found that these accounted for 10.1% and 6.5% of all NHL, respectively. We evaluated a total of 780 patients with malignant lymphomas from 2002 to 2006 and found that extranodal NKL and PTCL comprised 5.0% (39/780) and 7.4% (58/780) of all cases

**DIFFERENTIAL DIAGNOSIS**

**Angioimmunoblastic T Cell Lymphoma**

Given the presentation of type B symptoms, rash, lymphadenopathy, differential diagnoses include cutaneous lymphoid neoplasms (including cutaneous lymphomas), infections, an autoimmune disease. The pathological examination of suspicious lesions clinches the diagnosis.

**Large Cell Cutaneous Ki-1 Anaplastic Lymphoma**

Differential diagnosis includes Hodgkin's lymphoma and T-cell lymphomas, in which CD30 can be expressed.

**Cutaneous T-cell Lymphoma**

Benign dermatoses seem to be the most prominent differential diagnoses for cutaneous T-cell lymphomas. These conditions include psoriasis, contact dermatitis, drug eruption. Several of these benign dermatoses may even have T-cell rearrangements (TCR).

REFERENCES

<https://pmc.ncbi.nlm.nih.gov/articles/PMC3018617/>

<https://lymphoma.org/understanding-lymphoma/aboutlymphoma/nhl/ptcl/>

[Peripheral T-Cell Lymphoma: Symptoms, Causes & Prognosis](https://my.clevelandclinic.org/health/diseases/25103-peripheral-t-cell-lymphoma)

<https://www.ncbi.nlm.nih.gov/books/NBK562301/#article-17572.s8>

# 

# Lymphoma of the Skin

**Definition and description**

Skin lymphoma is a cancer that starts in lymphoid tissue in your skin.

When a non-Hodgkin lymphoma starts only in the skin (not in other organs or tissues) it is called a skin lymphoma (or cutaneous lymphoma).

A lymphoma that starts in lymph nodes or another part of your body and then spreads to your skin is not a skin lymphoma, because it didn’t start there.

## The lymph system and lymphoid tissue

To understand lymphoma, it helps to know something about the lymph system (also known as the lymphatic system).

Your lymph system is part of your immune system, which helps fight infections and some other diseases. Your lymph system also helps fluids move around your body.

### Lymphocytes

The lymph system is made up mostly of lymphocytes, a type of white blood cell. The main types of lymphocytes are:

* B lymphocytes (B cells): B cells normally help protect your body against germs (bacteria or viruses) by making proteins called antibodies. The antibodies attach to the germs, marking them for destruction by other parts of your immune system.
* T lymphocytes (T cells): There are several types of T cells, each with a special job. Some T cells destroy germs or abnormal cells in your body. Other T cells help boost or slow the activity of other immune system cells.
* Natural killer cells (NK cells): These cells destroy certain germs, such as viruses, as well as cells infected by viruses, and some cancer cells.

Any type of lymphocyte can develop into lymphoma. In the skin, T-cell lymphomas are more common than B-cell lymphomas. NK-cell lymphomas are rare.

Doctors can tell B cells, T cells, and NK cells apart with lab tests. These tests detect certain proteins on their surfaces and certain features of their DNA. The tests can also recognize several stages of B-cell, T-cell, and NK cell development.

This information helps doctors figure out which type of lymphoma you have and what your treatment options are.

### Lymphoid tissue

Most lymphocytes are in lymph nodes. But they can also be found in your blood and in lymphoid tissues throughout your body.

Lymphoid tissues are in your:

* Skin
* Spleen
* Bone marrow (the soft, inner parts of certain bones)
* Thymus
* Adenoids and tonsils
* Digestive tract
* Other organs

Skin lymphoma starts in lymphoid tissue in your skin.

Lymphomas can start in any part of your body that contains lymphoid tissue. Some types of lymphoma start in other parts of the body and then spread to the skin. But these are not the same as skin lymphomas, which always start in the skin.

# Risk Factors for Lymphoma of the Skin

A risk factor is anything that increases your chance of getting a disease like cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be changed. Others, like your age or family history, can’t be changed.

But having a risk factor, or even several, doesn’t mean that you will get the disease. And many people who get the disease may have few or no known risk factors.

While most people with lymphoma of the skin may have some risk factors (such as their age or sex), in most people there is no clear cause of the lymphoma.

## Older age

Age is an important risk factor for lymphoma of the skin.

* Most skin lymphomas happen in people in their 50s and 60s.
* But some types of skin lymphoma can appear in younger people, even in children.

## Sex

Most (but not all) types of skin lymphoma are more common in men than in women.

## Race

Most skin lymphomas tend to be more common in Black people than in White people. The reasons for this are not known.

## Having a weakened immune system

Skin lymphomas appear to be more common in people with weakened immune systems.

This includes people with acquired immunodeficiency syndrome (AIDS), as well as people who’ve had an organ transplant (such as heart, kidney, or liver) who must take drugs that suppress their immune system.

## Certain infections

Infection with certain viruses or other germs has been suggested as a possible cause of some skin lymphomas.

### HTLV-1 virus

Infection with the HTLV-1 virus has been linked with the rare adult T-cell leukemia/lymphoma, although most people infected with this virus don’t develop lymphoma. This infection is most often seen in parts of Japan and the Caribbean.

### Epstein-Barr virus (EBV)

Infection with Epstein-Barr virus (EBV) has been linked with some types of lymphoma, including extranodal NK/T-cell lymphoma, nasal type. But EBV infection is common, and most people infected with EBV do not go on to develop lymphoma.

### Borrelia

In parts of Europe (but not in the United States), infection with *Borrelia*, the bacteria that causes Lyme disease, has also been linked with some skin lymphomas.

This link has only been reported in a small number of cases. Most people with skin lymphoma have not had Lyme disease, and most people with Lyme disease do not develop lymphoma of the skin.

### Human immunodeficiency virus (HIV)

Infection with the human immunodeficiency virus (HIV), the virus that causes AIDS, may increase a person’s risk of skin lymphoma by weakening their immune system.

Some studies have suggested that infections with other viruses might also be linked with skin lymphomas, but more research is needed on this.

# Causes of Lymphoma of the Skin

Some risk factors can make a person more likely to get lymphoma of the skin, but it’s not always clear exactly how these factors might increase risk.

## Changes in genes can lead to cancer

Cancer (including lymphoma of the skin) is caused by changes in the DNA inside our cells. DNA is the chemical in our cells that makes up our genes, which control how our cells function.

Our DNA, which comes from both our parents, affects more than just how we look.

Different genes have different functions. Some genes normally help control when our cells grow, divide to make new cells, or repair mistakes in DNA. They also cause cells to die when they’re supposed to.

If these genes aren’t working properly, it can lead to cells growing out of control. For example:

* Oncogenes: Changes in genes that normally help cells grow, divide, or stay alive can lead to these genes being more active than they should be, causing them to become oncogenes. These genes can result in cells growing out of control.
* Tumor suppressor genes: Genes that normally help keep cell division under control or cause cells to die at the right time are known as tumor suppressor genes. Changes that turn off these genes can result in cells growing out of control.
* DNA repair genes: Some genes normally help detect and repair mistakes in a cell’s DNA. Changes that turn off these DNA repair genes can result in the buildup of DNA changes within a cell, which might lead to them growing out of control.

Any of these types of DNA changes might lead to cells growing out of control, which could lead to cancer.

**Are skin lymphoma gene changes inherited from a parent?**

Some people inherit DNA mutations (changes) from a parent that increase their risk of developing some types of cancer. But lymphoma of the skin is not one of the cancer types often caused by inherited mutations.

DNA changes related to lymphoma of the skin are usually acquired during life, rather than being inherited.

### Acquired gene changes

Some of these acquired changes may have outside causes (such as infections), but they often happen for no apparent reason. They seem to happen more often as we age, which may help explain why most types of skin lymphomas usually occur in older people.

Scientists are learning about the exact gene changes that cause skin lymphomas. But even though they have found some of these gene changes, they still don’t know why these changes occur.

## The role of the immune system in skin lymphomas

Lymphomas develop from cells called lymphocytes, which are part of the body’s immune system. Perhaps not surprisingly, some factors that affect the immune system seem to raise a person’s risk of skin lymphomas (and other lymphomas).

### People with weakened immune systems

People with weakened immune systems (such as people with acquired immunodeficiency syndrome (AIDS) and people who’ve had an organ transplant) seem to have a greater chance of developing skin lymphoma, but it’s not clear why.

### Some types of infections

Some types of infections also seem to raise the risk of skin lymphomas. This might be because the infections force the body’s immune system to constantly be active. As more lymphocytes are made to fight the infection, there is a greater chance that some of these cells will have DNA mutations in key genes, which might eventually lead to lymphoma. Researchers are still studying this.

## Signs and symptoms on the skin

Skin lymphomas can appear as:

* Papules (small, pimple-like lesions)
* Patches (flat, rash-like areas)
* Plaques (thick, raised or lowered lesions, often with distinct edges)
* Nodules or tumors (larger lumps or bumps under the skin)

These areas are often itchy, scaly, and red to purple in color.

People might also have hair loss in areas affected by the lymphoma. Sometimes, larger lesions can break open (ulcerate).

The lymphoma might show up as more than one type of lesion and on different parts of the skin. Skin lymphomas often happen in areas not exposed to the sun.

Some skin lymphomas appear as a rash over some or most of the body (known as erythroderma).

## Other possible signs and symptoms of skin lymphoma

Along with skin problems, in rare cases lymphoma of the skin can cause general symptoms, such as:

* Unexplained weight loss
* Fever
* Excessive sweating (enough to soak clothing), especially at night

Sometimes a skin lymphoma can reach the lymph nodes (small, bean-sized collections of immune cells), which can make them bigger.

An enlarged lymph node might be felt as a lump under the skin in the neck, underarm, or groin area.

## If you have symptoms, get them checked

Most of these symptoms are more likely caused by other, less serious conditions. Still, if you have any of them it's important to get checked by a doctor so the cause can be found and treated, if needed.

# Can Lymphoma of the Skin Be Found Early?

This type of lymphoma first appears in the skin, so it is usually found earlier in the course of the disease than many other types of cancer.

Skin lymphomas often look like other, more common skin problems such as infections or eczema, so it’s sometimes hard even for experienced doctors to diagnose this disease right away.

### See a doctor if you notice possible symptoms

The best approach is to see a doctor if you notice signs or symptoms that might be from a skin lymphoma (or another type of skin cancer).

This includes any new lesion (abnormal area) on the skin, especially if the lesion:

* Is raised
* Breaks open or bleeds
* Doesn’t go away
* Is growing

# Tests for Lymphoma of the Skin

Because this type of lymphoma affects the skin, it is often noticed fairly quickly. But the actual diagnosis of skin lymphoma can sometimes be delayed because the symptoms often resemble other, more common skin problems.

A skin lymphoma diagnosis can only be confirmed with a skin biopsy (described below). Other tests might be needed as well.

## Medical history and physical exam

If you have signs or symptoms of a possible skin lymphoma, your health care team will take your medical history and do a physical exam.

### Medical history

Your health care team will ask about your symptoms, possible risk factors, family history, and other medical conditions.

They will ask:

* When did you first notice the skin changes?
* Have they changed in size or appearance?
* Are they itchy or painful?

You may be asked if you have any other symptoms, like fever or weight loss.

Allergies and other causes:

Skin lymphomas can be hard to tell apart from allergies and other causes of rashes.

You might be asked if you have any allergies or if you’ve recently been exposed to something else that could cause skin problems, like new medicines, laundry detergents, creams, or lotions.

### Physical exam

During the physical exam, your health care provider will note the size, shape, color, and texture of any area(s) of skin in question. Your body will be checked all over for any other abnormal areas on your skin.

They might also feel the lymph nodes under the skin in your neck, underarms, or groin. Lymph nodes are small, bean-sized collections of immune cells. Lymphomas can sometimes cause them to become enlarged.

Referral to a dermatologist

If you are being seen by your primary doctor, you may be referred to a dermatologist (a doctor who treats skin diseases), who will look at your skin more closely.

## Skin biopsies

A biopsy is needed to diagnose lymphoma of the skin. This is a procedure in which a doctor removes a sample of body tissue for viewing under a microscope or other lab tests.

There are several types of skin biopsies. The type of biopsy you have will depend on your situation. Usually, a skin biopsy is done by a dermatologist.

### Punch biopsy

For a punch biopsy, the doctor uses a tool that looks like a tiny round cookie cutter. Once the skin is numbed with a local anesthetic, the doctor rotates the punch biopsy tool on the skin until it cuts through all the layers. The piece of skin is then removed.

Often, the biopsy site is closed with stitches.

### Incisional and excisional skin biopsies

For these biopsies, a surgical knife is used to cut through the full thickness of skin (usually in the shape of an ellipse, or oval).

* An incisional biopsy removes only part of the tumor.
* An excisional biopsy removes the entire tumor.

The piece of skin is removed for testing, and the edges of the cut skin are sewn together. These biopsies are usually done using a local anesthetic (numbing medicine).

### Testing skin biopsy samples in the lab

After the skin biopsy samples are removed, they are sent to the lab, where a doctor called a pathologist looks at them with a microscope.

The pathologist might do other tests on the biopsy samples as well.

Many of the more common forms of skin cancer (and other skin diseases) can be diagnosed just by looking at the biopsy samples. But diagnosing and classifying lymphomas of the skin often requires one or more special lab tests. Diagnosing some forms of skin lymphoma can be very challenging.

Sometimes, especially if the diagnosis is unclear, the skin samples may need to be sent to a:

* Dermatopathologist: A dermatologist or a pathologist with additional training in diagnosing skin samples
* Hematopathologist: A pathologist with additional training in diagnosing lymphomas

Even with this expertise, several biopsies may need to be done in different areas of abnormal skin and/or at different times before the diagnosis is confirmed.

## Lymph node biopsies

Skin lymphomas often spread to lymph nodes, so your doctor may recommend a lymph node biopsy to help confirm the diagnosis or help determine how widespread the lymphoma is.

This is more likely to be done if the doctor detects enlarged lymph nodes during a physical exam or imaging tests.

**Excisional or incisional lymph node biopsies**

These are the most common types of lymph node biopsy. In these procedures, a surgeon cuts through your skin to remove either:

* The entire lymph node (excisional biopsy)
* A small part of a large tumor (incisional biopsy)

If the node is just under your skin, this can often be done with local anesthesia (numbing medicine). But if the node is inside your chest or abdomen, you will need to be in a deep sleep (under general anesthesia) or deeply sedated during the biopsy.

Removing a lymph node almost always provides enough tissue to diagnose the exact type of lymphoma. Most doctors prefer this type of biopsy if it can be done without too much discomfort.

### Needle biopsy

For a needle biopsy, the doctor uses a thin, hollow needle to remove a small amount of tissue from a tumor. This can be done as either a:

* Fine needle aspiration (FNA), using a very thin needle
* Core needle biopsy, using a slightly larger needle

If an enlarged node is just under the skin, the doctor can aim the needle while feeling the node. If the enlarged node is deep inside the body, the doctor can guide the needle while viewing it with an imaging test such as an ultrasound or a CT scan.

The advantage of a needle biopsy is that it doesn’t require surgery. But sometimes this type of biopsy (especially an FNA) might not remove enough tissue to make a definite diagnosis of lymphoma.

However, advances in lab tests (discussed later in this section) and the growing experience of many doctors have improved the accuracy of this procedure.

## Other types of biopsies

Other biopsies are sometimes done to confirm a diagnosis of lymphoma. But more often, these procedures are used to help determine the stage (extent) of a lymphoma that has already been diagnosed.

Not everyone with lymphoma of the skin needs these tests.

### Bone marrow aspiration and biopsy

These tests are sometimes done after lymphoma is diagnosed to help figure out if it has spread to the bone marrow (the soft, inner part of certain bones). The two tests are often done at the same time.

The samples are usually taken from the back of the pelvic (hip) bone, but sometimes they are taken from other bones.

#### Bone marrow aspiration

For this procedure, you lie on a table (either on your side or on your belly). The doctor cleans the skin over your hip and then numbs the area and the surface of the bone by injecting a local anesthetic. This may cause a brief stinging or burning sensation.

A thin, hollow needle is then inserted into the bone, and a syringe is used to suck out a small amount of liquid bone marrow. Even with the anesthetic, most people still have some brief pain when the marrow is removed.

#### Bone marrow biopsy

A bone marrow biopsy is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is pushed down into the bone. This may also cause some brief pain. Once the biopsy is done, pressure is applied to the site to help stop any bleeding.

### Lumbar puncture (spinal tap)

This test looks for lymphoma cells in cerebrospinal fluid (CSF). CSF is the liquid that bathes your brain and spinal cord. Most people with skin lymphoma won’t need this test. But doctors may order it if a person has symptoms that suggest the lymphoma might have reached the brain.

For this test, you may be asked to lie on your side or sit up. The doctor first numbs an area in your lower back, over your spine. A small, hollow needle is then inserted between the bones of the spine to withdraw fluid.

## Lab tests of biopsy or blood samples

To help diagnose lymphoma and determine what type it is, lab tests are done on the biopsy samples. In some cases, blood samples are also tested.

Pathologists can sometimes tell which kind of lymphoma a person has just by looking at the cells under a microscope. But usually, they need other lab tests to confirm the diagnosis.

### Flow cytometry and immunohistochemistry

For both of these tests, cells from the biopsy samples are treated with special antibodies that stick to certain proteins on the cells.

* For immunohistochemistry (IHC), the cells are then looked at with a microscope to see if the antibodies stuck to them (meaning they have these proteins).
* For flow cytometry, a special machine passes the cells through a laser beam to analyze them.

These tests can help tell whether a lymph node is swollen because of lymphoma, some other cancer, or a non-cancerous disease.

Different types of lymphoma cells have different proteins on their surface, so these tests can also be used for immunophenotyping (determining which type of lymphoma a person has based on certain proteins in or on the cells).

### Chromosome and gene tests

Chromosomes are long strands of DNA that contain our genes.

Normal human cells have 23 pairs of chromosomes. Each chromosome is usually a certain size and looks a certain way. But in some types of lymphoma, the cells have changes in their chromosomes, such as having too many, too few, or abnormal chromosomes.

These changes can often help identify the type of lymphoma.

#### Cytogenetics (karyotyping)

Cells are looked at with a microscope to see if the chromosomes have any abnormalities. The cells need to be grown in the lab first, so results can take a week or more.

#### Fluorescent in situ hybridization (FISH)

This test looks more closely at lymphoma cell DNA using special fluorescent dyes that only attach to specific genes or parts of chromosomes.

FISH can find most chromosome changes that can be seen in standard cytogenetic tests, as well as some gene changes too small to be seen with cytogenetic testing. FISH is very accurate and can usually provide results within a couple of days.

#### Other molecular and genetic tests

Other types of lab tests can also be done on the samples to look for specific gene changes or other changes in the lymphoma cells.

Many of these tests are done using next-generation sequencing (NGS), which can look for changes in many different genes at once. This type of testing usually takes a week or longer to get results.

## Blood tests

Blood tests measure the amounts of certain types of cells and chemicals in the blood. They are not usually used to diagnose lymphoma, but they can sometimes help determine how advanced the cancer is.

Blood tests may also be used during certain types of treatment (such as chemotherapy) to monitor how well the bone marrow and other organs are working.

### Complete blood count (CBC)

This test measures the levels of different cells in the blood, such as red blood cells, white blood cells, and platelets. The CBC is often done with a differential (“diff”), which counts the numbers of different types of white blood cells.

* If a person’s blood counts are low, it might mean the lymphoma is growing in the bone marrow and slowing normal blood cell production.
* People with Sezary syndrome will have Sezary cells in their blood. These can be found on the differential.
* People getting chemo will have their blood counts checked regularly to see if the treatment is affecting their bone marrow.

### Blood chemistry tests

These tests look at how well organs such as the kidneys and liver are working. Blood chemistry tests are also done regularly in people getting chemo.

### LDH levels in the blood

If you’ve been diagnosed with lymphoma, the levels of lactate dehydrogenase (LDH) in your blood may be checked. LDH levels are often abnormally high in people with widespread lymphoma.

### Blood tests to check for infection

For some types of lymphoma, or for certain treatments, your doctor may also suggest tests to see if you’ve been infected with certain viruses, such as:

* Hepatitis B virus (HBV)
* Hepatitis C virus (HCV)
* Human T-cell lymphotropic virus (HTLV-1)
* Human immunodeficiency virus (HIV)

Infections with these viruses might affect your treatment.

## Imaging tests

Imaging tests use x-rays, sound waves, magnetic fields, or radioactive particles to make pictures of the inside of the body. In someone with known or suspected skin lymphoma, these tests might be done for different reasons, including:

* To learn how far the lymphoma has spread
* To find out if treatment is working
* To look for possible signs of the lymphoma coming back after treatment

Imaging tests aren’t always needed for people with skin lymphomas who have only a few skin lesions. But imaging is often done if a lot of the skin is affected, or if lymphoma cells are found in the lymph nodes or blood.

### Chest x-ray

An x-ray of the chest may be done to look for enlarged lymph nodes in this area.

### Computed tomography (CT) scan

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

When looking for lymphoma in the body, CT scans are often combined with a PET scan (known as a PET/CT scan, see below).

#### CT-guided needle biopsy

A CT scan can also be used to guide a biopsy needle into a suspicious area.

For this test, you lie on the CT scanning table while the doctor advances the needle through your skin and toward the area. The scans are repeated until the needle is in the right place. A biopsy sample is then removed and sent to the lab.

### Magnetic resonance imaging (MRI)

Like CT scans, MRIs show detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. MRI scans are very helpful for looking at the brain and spinal cord, but they are not often used to evaluate skin lymphomas unless a CT scan can’t be done for some reason.

### Ultrasound

Ultrasound can be used to look at lymph nodes near the surface of the body. It can also be used to look inside your abdomen for enlarged lymph nodes or organs, such as the liver and spleen. (It's harder to use it to look at organs or lymph nodes in the chest because the ribs block the sound waves.)

This test uses sound waves and their echoes to create images, so there is no radiation. You simply lie on a table and a technician moves a small, hand-held device called a transducer over the part of your body being looked at.

#### Ultrasound-guided needle biopsy

Ultrasound can also be used to guide a biopsy needle into a suspicious area inside your body, such as an enlarged lymph node. A biopsy sample is then removed and sent to the lab.

### Positron emission tomography (PET) scan

For a PET scan, you are injected with a slightly radioactive form of sugar, which collects mainly in cancer cells. A special camera then creates a picture of areas of radioactivity in your body. It can show possible areas of lymphoma in all areas of your body at once.

A PET scan can be used to:

* Help tell if an enlarged lymph node contains lymphoma or is benign
* Spot small areas that might be lymphoma, even if the areas look normal on a CT or MRI scan
* See if an advanced skin lymphoma is responding to treatment

Some doctors will repeat the PET scan after a few courses of chemotherapy. If the chemo is working, the abnormal areas will no longer take up the radioactive sugar.

#### PET/CT scan

The picture from a PET scan isn't as detailed as those from a CT or MRI scan. But doctors often use a machine that does both a PET and CT scan at the same time (PET/CT scan).

This lets the doctor compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT scan.

# Skin-directed Treatments for Skin Lymphomas

For many skin lymphomas (especially early-stage lymphomas), the first treatment is directed at the skin lesions themselves, while trying to avoid harmful side effects on the rest of the body.

There are many ways to treat skin lesions. Sometimes more than one type of treatment is used, either at the same time or one after another.

## Surgery

Surgery is not usually used by itself to treat skin lymphoma, but it can be helpful in some situations.

* Biopsy: Surgery may be used to biopsy a skin lesion, lymph node, or other tissue to diagnose and classify a lymphoma.
* Treatment: Surgery is sometimes part of treatment for certain types of skin lymphomas if there are no more than a few skin lesions and those lesions can be removed completely. If surgery is done, it is often combined with other types of treatment.

## Radiation therapy

Radiation therapy uses high-energy rays to kill cancer cells. The treatment is much like getting an x-ray, but the radiation is stronger. The procedure itself is painless. Treatment might be given in just one dose or on several days, depending on how much of the skin is being treated.

### Electron beam radiation

Electron beam radiation is the type of radiation used most often for skin lymphomas.

The beam of electrons only penetrates as far as the skin, so there are few side effects to other organs and tissues. The main possible side effect of electron beam therapy is a skin reaction similar to a sunburn.

### Total skin electron beam therapy (TSEBT)

For mycosis fungoides and Sezary syndrome covering a large part of the skin, electron beam therapy is sometimes given to the entire body. This is called total skin electron beam therapy (TSEBT).

Along with skin changes, this can sometimes cause loss of all hair on your body, dry skin, a reduced ability to sweat for several months, and even the loss of fingernails and toenails. However, any of these structures can be shielded if they don’t need to be treated.

### High-energy radiation (x-rays or gamma rays)

Some thicker lymphomas that are not widespread (especially single lesions) are treated with high-energy radiation (like x-rays or gamma rays) instead of electrons.

This kind of radiation can penetrate deeper into the body. Because it can damage internal organs, the treatment is planned carefully so that most of the radiation goes only to the skin.

## Phototherapy (UV light therapy)

Ultraviolet (UV) light is the higher-energy part of sunlight that causes sunburn and can lead to skin cancer. Phototherapy uses UV light to kill cancer cells in the skin. This is a useful treatment for some skin lymphomas that aren’t very thick, especially if they involve large areas of the skin.

Ultraviolet A (UVA) and ultraviolet B (UVB) can be used to treat skin lymphoma. Both UVA and UVB treatments are given with special fluorescent lamps like those used in tanning salons.

Just like the UV light in sunlight, these treatments can cause sunburn and may raise the risk of skin cancer later in life, so doctors try to avoid giving too much UV light. During treatment, your radiation team carefully controls the wavelength and dose of light to minimize your risk of burns.

Treatments are given several times a week.

### Psoralens and UVA (PUVA)

When UVA is used, it is combined with drugs called psoralens. This combination is referred to as PUVA.

Psoralens are given as a pill about 2 hours before the treatment. The drug travels through your blood to reach cells throughout your body (including cells of skin lymphoma). When these cells are exposed to UVA light, the drug is activated, killing them.

Psoralens can cause some nausea. They can also make your skin and eyes very sensitive to sunlight, increasing the risk of severe skin burns and cataracts. It's important to protect yourself from sunlight as much as possible in the days after treatment.

### Narrowband UVB (NB-UVB)

UVB (sometimes described as narrowband UVB, or NB-UVB) is given without any extra medicines. It is generally used for thinner skin lesions.

## Topical medicines

Treatment that applies drugs directly to the skin is called topical therapy. It can be very helpful in treating many early skin lymphomas.

When a drug is put on your skin, its effects are concentrated on that spot, with much smaller amounts reaching the rest of your body. This can help limit side effects, especially for strong medicines such as some chemotherapy drugs.

### Topical corticosteroids

These are drugs related to cortisol, a hormone made naturally in the body that can affect immune cells such as lymphocytes (the cells lymphomas start from).

Corticosteroid pills and injections into the blood have long been an important part of treating lymphomas. Topical forms of these drugs can also be applied directly to the skin as ointments, gels, foams, and creams (usually once or twice a day), or injected directly into skin lesions on a less frequent basis.

Long-term use of topical corticosteroids may cause the skin in that area to become thinner.

### Topical chemotherapy drugs

Chemotherapy (chemo) drugs are medicines often given by mouth or injected into a vein to treat more advanced cancers, including advanced skin lymphomas.

Some chemo drugs can be used to treat earlier forms of skin lymphoma by putting them directly on the skin, usually as a cream, ointment, or gel.

The drug most often used to treat skin lymphoma is mechlorethamine (nitrogen mustard). Possible side effects include redness, swelling, or irritation where the drug is applied, as well as an increased risk of other types of skin cancer in the area.

### Topical retinoids

Retinoids are drugs related to vitamin A. By affecting certain genes in lymphoma cells, they can help them mature.

Some retinoids, such as bexarotene (Targretin), come in a gel that is applied directly to skin lesions. Possible side effects include redness, itching, irritation, and sensitivity to sunlight in the area where the drug is applied.

These drugs can cause birth defects, so they should not be used if you are pregnant or could become pregnant.

### Topical immunotherapy

Imiquimod (Zyclara) is a cream that causes an immune system reaction when applied to skin lesions, which may help destroy them. This drug is used mainly to treat other types of skin cancer, but some doctors may also use it to treat early forms of skin lymphoma.

It can cause redness, itching, and irritation where it is applied.

# Treatment for Specific Types of Skin Lymphoma

The treatment you get for skin lymphoma will depend mainly on the type of lymphoma you have, its location, and its stage (how far it has spread). But other things can also affect your treatment options, such as your overall health.

The treatments mentioned here fall into 2 main groups:

* Skin-directed treatments
* Whole-body (systemic) treatments

Along with treatments aimed at the lymphoma itself, supportive care treatments for symptoms such as itching or skin infections are also an important part of care for many people with skin lymphomas. This type of treatment is often given by a dermatologist, a doctor who treats diseases of the skin.

## Mycosis fungoides (MF)

Many forms of treatment can be used for mycosis fungoides (MF).

### Skin-directed treatments for MF

For early stages of MF, treatments are aimed at the skin. Sometimes more than one type of skin-directed treatment is used.

Options may include:

* Phototherapy with ultraviolet (UV) light, either UVB light or UVA combined with drugs called psoralens (known as PUVA)
* Topical chemotherapy with nitrogen mustard
* Topical corticosteroid ointments or injections
* Topical retinoids (vitamin A-like drugs), such as bexarotene
* Topical imiquimod (a form of immunotherapy)
* Local radiation treatments, if there are no more than a few lesions
* Total skin electron beam therapy (TSEBT), if MF covers most of the skin

### Systemic (whole-body) treatments for MF

MF might stay just in the skin for many years. But eventually it might spread, which could require systemic treatment.

Several types of treatment can be used, such as:

* Retinoids (taken by mouth)
* Targeted drugs like vorinostat (Zolinza) or romidepsin (Istodax)
* Photopheresis
* Interferons
* Brentuximab vedotin (Adcetris)
* Mogamulizumab (Poteligeo)
* Pembrolizumab (Keytruda)
* Low-dose methotrexate (a chemo drug)

Chemotherapy (usually with a single drug) or other medicines might also be an option. But these treatments are often reserved for lymphomas that are no longer responding to the treatments above.

If single chemo drugs are not effective, combinations of drugs might be recommended (similar to those used for other types of non-Hodgkin lymphoma).

### Combining treatments for MF

More than one type of treatment might be used at the same time. This could include:

* Combinations of skin-directed and systemic treatments (such as TSEBT plus photopheresis) or
* Combined systemic treatments (such as an oral retinoid plus interferon)

Many people can be helped by these treatments, sometimes for many years, but they rarely cure the lymphoma. If other treatments are no longer working, a stem cell transplant may be an option. Newer treatments are also being studied, so it might be worth considering entering a clinical trial.

## Sezary syndrome

The systemic treatments used for advanced MF (see above) are also used to treat Sezary syndrome. This disease has usually spread beyond the skin at the time it is diagnosed, so treatments directed only at the skin are less useful than in MF (although some might still be part of treatment).

An important goal of treatment for Sezary syndrome is the relief of symptoms related to the disease, such as itching.

### Possible treatment options for Sezary syndrome

Photopheresis may be helpful in treating the disease, as may retinoids such as bexarotene. The targeted drugs vorinostat (Zolinza) and romidepsin (Istodax) might also be used, as might interferon, brentuximab vedotin (Adcetris), or mogamulizumab (Poteligeo).

Chemotherapy or other drugs such as alemtuzumab or pembrolizumab (Keytruda) might also be useful, but these are usually reserved for lymphomas that are no longer responding to other treatments.

A stem cell transplant might be another option if other treatments are no longer working.

As with advanced MF, these treatments are often helpful for a time, but they rarely result in a cure. Newer treatments are now being studied, so it might be worth considering entering a clinical trial.

## Primary cutaneous anaplastic large cell lymphoma (C-ALCL)

This lymphoma usually stays confined to the skin. It can come back after treatment, but it seldom spreads inside the body and is rarely fatal.

If it isn’t causing symptoms, it can often be watched closely without needing to be treated right away. The skin lesions may even go away on their own, without any treatment.

### Possible treatment options for C-ALCL (if needed)

If treatment is needed, options depend on how extensive the lymphoma is:

* For single skin lesions (or small groups of lesions), surgery and/or radiation therapy are the most common options.
* If skin lesions are in several places, the targeted drug brentuximab vedotin (Adcetris) or chemotherapy (often methotrexate, taken as a pill) is often the first treatment.
* Other chemotherapy, targeted therapy, or retinoid drugs might also be options, as well as radiation therapy (and possibly other skin-directed treatments).

### If C-ALCL comes back or spreads

If the lymphoma comes back in the same place after treatment, the same treatment can often be used again. If one treatment is no longer helpful, another can be tried.

If the lymphoma spreads to the lymph nodes or (rarely) internal organs, brentuximab vedotin (Adcetris), chemotherapy, or a combination of the two might be an option. Sometimes radiation therapy might be given as well.

## Lymphomatoid papulosis

This disease often comes and goes on its own. It usually has such a good outlook that treatment isn't needed right away, especially if the lesions aren't causing symptoms.

If treatment is needed, options depend on how extensive it is:

* If there are only a few skin lesions, topical corticosteroids or﻿ phototherapy are the most common treatments.
* If the lesions are more extensive, skin-directed treatments are an option (phototherapy, topical chemotherapy, or corticosteroids). Systemic treatments such as oral retinoids or low-dose methotrexate are also an option.

More intensive systemic therapies are rarely needed.

## Subcutaneous panniculitis-like T-cell lymphoma

People with this rare type of skin lymphoma can live a long time and generally have an excellent outlook. The disease can often be controlled for long periods with corticosteroids or other medicines that suppress the immune system.

Chemotherapy, radiation, stem cell transplant, or newer treatments might also be options, if needed.

## Primary cutaneous peripheral T-cell lymphoma, rare subtypes

* Primary cutaneous gamma/delta T-cell lymphoma tends to grow and spread very quickly. It is treated with systemic chemotherapy using a combination of drugs, but even with treatment it can often be hard to control.
* Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma usually grows quickly and is treated with systemic chemotherapy using a combination of drugs. Even with treatment, it can often be hard to control.
* Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder tends to grow slowly, and it can usually be treated effectively with surgery or radiation therapy. It sometimes comes back, but it can often be treated again in the same way.
* Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder sometimes goes away on its own. If treatment is needed, it is usually surgery or radiation therapy, or a corticosteroid injected into the tumor. People with this lymphoma generally have a very good outlook, especially if they have only one tumor.

Some of these lymphomas can be hard to treat effectively, so clinical trials studying newer forms of treatment might be a good option.

## Primary cutaneous marginal zone B-cell lymphoma OR primary cutaneous follicle center lymphoma

These types of skin lymphoma tend to have a good outlook. They can sometimes be watched without treatment until problems develop, but treatment is usually recommended.

### Lymphomas in one spot or only a few spots close together

Initial treatment is usually radiation therapy or surgery.

Other options might include topical medicines such as corticosteroids, topical chemotherapy, bexarotene (Targretin), or imiquimod (Zyclara). Injected corticosteroids might also be used.

If the lymphoma doesn’t go away completely with one of these treatments, another one can be tried.

### Lymphomas that have spread over larger parts of the skin

Treatment options include rituximab (Rituxan), injected corticosteroids, radiation therapy, or topical medicines such as corticosteroids, topical chemotherapy, bexarotene, or imiquimod.

If there are many lesions, systemic chemotherapy (sometimes with rituximab) can also be used, similar to treatment for other slow-growing B-cell lymphomas.

### Lymphomas that have spread to lymph nodes or internal organs

In this case, the lymphoma is treated like follicular lymphoma or marginal zone lymphoma found in other parts of the body, such as with a combination of chemotherapy and rituximab.

## Primary cutaneous diffuse large B-cell lymphoma, leg type

At first, these lymphomas might look like they involve only a small area of the skin, often on the legs. But the disease is often more widespread than it appears.

The treatment of choice is usually rituximab (Rituxan) along with systemic chemotherapy. Often the regimen called R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is given, but other combinations can also be used.

If the lymphoma is in no more than a few areas, radiation therapy directed at the tumors is often used as well. For people who can’t get chemo for some reason, radiation therapy alone may be an option.

### If the lymphoma has spread to lymph nodes or other organs

If the lymphoma has spread to the lymph nodes or other organs, treatment is the same as that used for diffuse large B-cell lymphomas (DLBCLs) found in other parts of the body.

## If the lymphoma keeps growing or comes back after treatment

Some skin lymphomas respond well to treatment, but others do not. If this happens, other types of treatment can often be tried. But as more treatments are tried, they may cause more side effects and be less likely to work.

When a cancer comes back after treatment, it is called recurrent or relapsed.

### Lymphoma that comes back in the skin

In general, if a skin lymphoma comes back it tends to be in the skin. If this is the case, skin-directed therapies that haven’t been used yet may be effective. Slow-growing skin lymphomas might just be watched closely unless they cause symptoms.

### Lymphoma that comes back in another part of the body

Some skin lymphomas eventually spread inside the body as well.

Often, the lymph nodes are the first site of relapse. After that, the lymphoma might spread to organs such as the liver, spleen, or bone marrow. Different types of systemic treatments may be helpful in this situation.

* Chemotherapy might be used, especially if a person hasn’t had chemo before.
* Depending on the type of lymphoma and treatments a person had before, other options might include drugs such as vorinostat (Zolinza), romidepsin (Istodax), brentuximab vedotin (Adcetris), mogamulizumab (Poteligeo), or pembrolizumab (Keytruda).
* A stem cell transplant may be another option at some point.

Advanced skin lymphomas can be very hard to cure. Different systemic treatments may work for a while. But usually, the more treatments a person has, the less likely it is that the next treatment will help.

A good option for some people might be to consider entering a clinical trial testing a newer type of treatment. Many newer treatments are now being studied.

# Prevention

Most lymphomas of the skin have no known cause, so there is no sure way to prevent them from developing.

Having a weakened immune system may raise your risk of skin lymphoma, so making sure your immune system stays healthy might be one way to limit your risk.

An example of this would be to avoid known risk factors for infection with HIV (the virus that causes AIDS), such as:

* Intravenous (IV) drug use
* Unprotected sex with someone whose HIV status is unknown

## Epidemiology

Cutaneous T-cell lymphoma has a worldwide distribution; some studies have identified a higher prevalence of the disease in industrial populations (eg, among workers who use machine cutting oils). The incidence of cutaneous T-cell lymphoma in the United States was reported to be 6.4 persons per million population annually (for the overall, age-adjusted incidence) between 1973 and 2002, with the disease’s incidence increasing over that time period.

Adult T-cell lymphoma/leukemia is endemic in areas with a high prevalence of HTLV-1 infection, such as southwest Japan, the Caribbean islands, South America, and parts of central Africa. This disease occurs in 1-5% of seropositive individuals after more than 2 decades of viral persistence.

Nasal-type NK/T-cell lymphoma, which is associated with Epstein-Barr virus (EBV) infection, is more common in Asia, Central America, and South America.

A study in Kuwait found that the annual incidence rate of mycosis fungoides there was 0.43 cases per 100,000 persons.

### Race-, sex-, and aged-related demographics

In the United States, cutaneous T-cell lymphoma is more common among persons of sub-Saharan African lineage than among those of European background, in a ratio of approximately 2:1. In Kuwait, a study found that the annual incidence rate of mycosis fungoides was significantly higher among Arabs than among non-Arab Asians.

Cutaneous T-cell lymphoma has a sex predilection, being more common in men than women by a ratio of approximately 2:1.

Most patients with cutaneous T-cell lymphoma are middle-aged or elderly. Sézary syndrome, for example, occurs almost exclusively in adults. Many patients have had a poorly defined form of dermatitis for many years prior to the onset of the disease. In a significant proportion of cases, the onset of the disease, or of a dermatitic precursor of the disease, occurs in childhood.

However, cutaneous T-cell lymphoma is exceedingly rare in children younger than 10 years, and in such cases it does not show a male predominance; one series even reported a strong female predilection. Similar to adult patients, most children present in stage IA or IB and have a good to excellent prognosis with treatment, although cases progressing to plaque, tumor-stage disease, and death have been reported.

Some patients with limited mycosis fungoides are described as having Woringer-Kolopp disease (pagetoid reticulosis). These patients are usually middle-aged, with an age distribution in one series ranging from 13-68 years and with a mean age of 55 years.

**DIFFERENTIAL DIAGNOSIS**

## Diagnostic Considerations

Cutaneous T-cell lymphomas are T-cell proliferative disorders. Primary cutaneous lymphomas require distinction from histologically similar primary nodal ones because their clinical behavior, prognosis, and therapy are often different. In addition, a difference often exists between primary cutaneous and nodal lymphomas in the presence of specific translocations.

At times, disseminated infections such as leishmaniasis, leprosy, South American blastomycosis, coccidioidomycosis, and other deep fungal infections may mimic and require distinction from cutaneous T-cell lymphoma. Acne vulgaris, epidermal inclusion cysts, and insect bites may resemble folliculotropic mycosis fungoides.

Granulomatous mycosis fungoides with hypohidrosis may mimic lepromatous leprosy.Other conditions to consider in the differential diagnosis of cutaneous t-cell lymphoma include non lymphomatous erythroderma and erythema neurolyticum migrans.

## Differential Diagnoses

* Allergic Contact Dermatitis
* Irritant Contact Dermatitis
* Lichen Planus
* Parapsoriasis
* Pediatric Atopic Dermatitis
* Pemphigus Foliaceus
* Plaque Psoriasis
* Pustular Psoriasis
* Tinea Corporis

### GUIDELINES FOR SKIN LYMPHOMA

### NHL Classification Schemas

This classification divides NHL into two groups: those of B-cell origin and those of T-cell/natural killer (NK)–cell origin.

Although considered obsolete, the National Cancer Institute’s Working Formulation (IWF) classification is still used, mainly for historical data comparisons.

The World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous T-cell lymphoma (CTCL) is divided into CTCLs with indolent clinical behavior and those with aggressive subtypes. CTCLs with indolent clinical behavior include the following:

* Mycosis fungoides
* Mycosis fungoides variants and subtypes (eg, folliculotropic mycosis fungoides, pagetoid reticulosis, granulomatous slack skin)
* Primary cutaneous CD30+ lymphoproliferative disorder (eg, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis)
* Subcutaneous panniculitis-like T-cell lymphoma (provisional)
* Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (provisional)

NCCN primary treatment recommendations for PC-ALCL, are as follows:

* For solitary or grouped lesions, surgical excision or radiation therapy for first-line treatment
* Relapses are equally frequent after both treatments; if confined to the skin, treatment can be repeated
* For multifocal lesions, brentuximab vedotin is the preferred treatment. Other recommended regimens with or without SDT include low dose methotrexate, retinoids, pralatrexate and observation, if asymptomatic.
* Interferon is an NCCN category 3 recommendation.

For PC-ALCL with regional node involvement (N1), brentuximab vedotin with or without ISRT is the preferred regimen. Other recommended treatments include:

* Brentuximab vedotin with CHP
* Methotrexate with or without ISRT
* Pralatrexate with or without ISRT
* CHOP or CHOEP with or without ISRT, in select cases

### NICE

After reviewing the clinical- and cost-effectiveness evidence for brentuximab vedotin for treating relapsed or refractory CD30-positive (CD30+) cutaneous T-cell lymphoma (CTCL), the National Institute for Health and Care Excellence (NICE) recommended brentuximab vedotin as a second-line treatment for treating CD30+ CTCL.

**REFERENCE**

<https://emedicine.medscape.com/article/2139720-overview#a6>

### 

### 

### CNS lymphoma

**Definition and description**

CNS lymphoma is a rare, aggressive cancer that develops in your central nervous system (CNS). Tumors may form in your brain, spinal cord, spinal fluid and (as it’s so close to your brain) your eye. It’s a type of non-Hodgkin lymphoma.

CNS lymphoma starts in white blood cells called lymphocytes, which are part of your lymphatic system. Your lymphatic system is an important part of your immune system. It helps your body fight infections and diseases. When the lymphoma starts in your CNS and isn’t found anywhere else in your body, it’s called primary CNS lymphoma. If lymphoma is in other parts of your body, as well as in your CNS, it’s called secondary CNS lymphoma.

Although anyone can get this cancer, you’re more likely to be diagnosed if you’re a male who has a weakened immune system from a condition like HIV and AIDS. People over 65 are also more at risk. Still, this cancer is extremely rare. Only about 1,500 new cases are diagnosed in the U.S. each year.

No matter your unique situation, your healthcare team will work with you to find the right treatment to fight CNS lymphoma.

## Symptoms and Causes

Symptoms depend on where the tumor is located. For instance, CNS lymphoma may not cause symptoms if it’s in the membrane covering your brain and spinal cord (meninges). But a tumor near your eyes often causes vision changes. If the mass occurs near the area of your brain that controls movement, you could have weakness or coordination changes.

Symptoms of CNS lymphoma may include:

* Nausea and vomiting
* Weakness in your arms, legs or face
* Weakness affecting one side of your body (hemiparesis)
* Hearing loss
* Difficulty swallowing (dysphagia)
* Signs of brain pressure (headaches, confusion)
* Vision problems (blurry vision, seeing double, floaters)
* Changes in your mental state (trouble speaking, memory loss, feeling sluggish)
* Seizures (that may become more frequent over several days or weeks)
* Trouble controlling when you pee or poop (urinary and fecal incontinence)

### causes of CNS lymphoma

Like other types of lymphoma, CNS lymphoma forms when cells in lymph tissue start to behave abnormally. They multiply out of control and overtake healthy cells. With CNS lymphoma, the cells that start growing abnormally are usually white blood cells (lymphocytes) called B cells.

Researchers aren’t sure what causes a lymphocyte to transform into a cancer cell. But they’ve identified factors that may increase your risk of CNS lymphoma.

### Risk factors for CNS lymphoma

Certain conditions associated with having a weakened immune system may increase your risk of CNS lymphoma. Risk factors include:

* HIV/AIDS (especially if you have an active Epstein-Barr infection)
* Wiskott-Aldrich syndrome (WIS)
* Common variable immunodeficiency state (CVID)
* Ataxia-telangiectasia
* Taking immunosuppressant drugs following an organ transplant

## Diagnosis and Tests

Your healthcare provider may recommend different procedures and tests to diagnose CNS lymphoma. Cancer staging also takes place during diagnosis. Cancer staging helps providers determine how advanced the cancer is and which treatments will likely work best.

You may need:

* Exams. Your provider will check the health of your brain, spinal cord and eyes. They’ll perform a neurological exam to check your CNS. They may do a slit lamp exam to find signs of a tumor behind your eye.
* Imaging tests. Your provider may order an MRI, CT scan or PET scan to see where cancer is located inside of your body. CNS lymphoma rarely spreads beyond your central nervous system, but it may spread quickly within it.
* Blood tests. Blood tests allow your provider to check your cells for signs of cancer. Tests include a complete blood count, blood chemistry study and an HIV test.
* Tissue and fluid tests. Your provider may remove a sample of fluid or tissue from your spinal fluid, bone marrow or the tumor itself to test for cancer cells.

## Management and Treatment

Not everyone agrees on the best treatment for CNS lymphoma. Instead, your healthcare team will suggest a care plan based on various factors, like your age, your HIV/AIDS status and whether the cancer is newly diagnosed or recurrent (returned after treatment). Treatment will likely involve a combination of therapies.

Treatments for CNS lymphoma include:

* Chemotherapy. Chemotherapy uses drugs to kill cancer cells. High doses of a chemotherapy drug called methotrexate (HD-MTX) are often used to treat newly diagnosed CNS lymphoma.
* Radiation. Radiation uses beams of energy to kill cancer cells. One type of radiation treatment for symptom relief is whole-brain radiation. It destroys cancer cells throughout your brain.
* Targeted therapy. Targeted therapy uses substances like proteins and antibodies to attack cancer cells. Rituximab and ibrutinib are targeted therapy treatments that your provider may recommend.
* Stem cell transplant. During a stem cell transplant, you receive healthy blood cells to replace blood cells damaged during cancer treatments like chemotherapy and radiation.
* Clinical trial. Your provider may recommend you take part in a clinical trial to test new treatments. Current trials are studying the effectiveness of new targeted therapy drugs and new combinations of chemotherapy drugs in CNS lymphoma treatment.

If you’re HIV-positive or have AIDS, you’ll continue antiretroviral therapy (ART) while you receive treatments for CNS lymphoma.

#### Complications/side effects of treatment

Treatments for CNS lymphoma can cause side effects that your healthcare provider will discuss with you beforehand. For example, whole-brain radiation destroys cancer cells in your brain. But it may also lead to several severe side effects that can impact your brain function. All treatment options pose potential risks.

Discuss the benefits and risks of your treatment plan with your provider. Ask if they recommend palliative care. This treatment can help you manage side effects and the overall impact cancer has on your life.

## Outlook / Prognosis

CNS lymphoma is a fast-spreading cancer that often returns following treatment. Still, your prognosis (chance of recovery) depends on several unique factors, including:

* Your age
* Your overall health
* Your HIV status
* The location of the tumor
* The result of your blood chemistry studies (which can tell how the cancer may be impacting your organs)

Your healthcare team will work with you to find the treatment plan that gives you the best chance of survival without sacrificing your quality of life.

#### survival rate for CNS lymphoma

Researchers report on cancer survival rates by tracking how many people with a certain cancer diagnosis are alive after a set time, usually five years. The five-year survival rate for people with CNS lymphoma is 30%. This means that 3 out of 10 people diagnosed with CNS lymphoma are alive five years later.

Still, these numbers are general. They don’t factor in other specifics that affect prognosis. For instance, outcomes are usually better if you’re not immunocompromised or if the lymphoma hasn’t spread beyond your brain. Survival rates also don’t consider the impact that new treatments may have on your life expectancy.

Your provider is your best resource for explaining how your health and unique cancer diagnosis will shape your likely outcome.

## Living With

Living with lymphoma is hard. You may feel anxious about what tests or treatments lie ahead. You may not know how to share what you’re feeling with others.

Now, more than ever is the time to reach out and take advantage of every available resource. This may mean reaching out to loved ones, even if it’s difficult. It may mean asking your healthcare provider about palliative care or support groups. Everyone’s cancer journey is different. But it’s essential to connect with others every step of the way.

### When should I see a doctor

Even when CNS lymphoma goes into remission (no signs or symptoms of cancer), you’ll need regular check-ups to see if the cancer comes back. You’ll need more frequent visits within the first five years of treatment. Most CNS lymphoma that recurs comes back within the first five years.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for this condition includes the following:

* The clinical presentation must guide thinking about the differential diagnosis.
* When facing known intraparenchymal disease, the chief differentials are other primary or secondary CNS neoplasms, such as high-grade gliomas and metastatic lesions.
* Whenever diffusion restriction is noted on MRI, cerebral infarct must be considered along with tumefactive demyelination or other causes of inflammatory lesions.
* When ring-enhancing lesions are noted in the setting of immunocompromise, toxoplasmosis, and fungal abscesses must be excluded.
* Tolosa Hunt syndrome, a painful ophthalmoplegia caused by nonspecific inflammation of the cavernous sinus or superior orbital fissure, exhibits clinical and radiographic features similar to PCNSL, including steroid responsiveness.

**Epidemiology**

CNS lymphoma is decreasing in persons living with AIDS due to the advent of HAART, but its incidence is rising in older adults. The disease is rare in pediatric populations. PCNSL has an annual incidence of approximately 1700 cases in the United States or approximately 0.5 per 100,000 per year. PNCSL comprises 3% of all primary brain tumors and 2% to 3% of all cases of NHL. Immunocompetent patients are often diagnosed between ages 50 and 70, whereas immunocompromised patients present earlier, typically in their 30s and 40s. Men are affected more than women in both immunocompetent and immunocompromised groups, though there is no sex-based predilection in patients who develop CNS lymphoma after solid organ transplantation. Other patient populations at risk for PCNSL include those with ataxia-telangiectasia, Wiskott-Aldrich syndrome, and other immunodeficiency syndromes.

The vast majority—more than 90%—of PCNSL cases are diffuse large B-cell lymphoma; primary forms of T-cell and Burkitt lymphomas and lower-grade lymphoproliferative conditions have also been reported. Within the CNS, PCNSL most commonly arises in the frontal lobe and the basal ganglia, with the brainstem, cerebellum, and spinal cord less commonly affected. Most immunocompetent patients have a solitary brain mass, with multiple lesions observed in 20% to 40% of cases.

Up to 25% of patients with PCNSL develop intraocular lymphoma, and primary intraocular lymphoma ultimately disseminates to the CNS more than 80% of the time. Concurrent cerebrospinal fluid (CSF) and orbit involvement occur in up to 20% of cases. Primary intraocular lymphoma predominates in the vitreous fluid and the retina. Beyond the orbit, PCNSL rarely disseminates systemically. Roughly 40% of systemic lymphomas arise in or near the CNS, including the paranasal sinuses and the previously mentioned localizations. Secondary CNS lymphoma preferentially affects the dura and leptomeninges; leptomeningeal metastases occur in 4% to 11% of patients with systemic lymphoma.

**COMPLICATION**

Several complications, such as gait impairment, memory loss, and incontinence, can arise in patients treated with WBRT. These most commonly occur in individuals older than 60. Reports also exist of post-traumatic stress disorders in individuals after treatment. The risk of developing a second malignancy increases in long-term CNS lymphoma survivors, particularly in younger age groups. Patients with secondary CNS lymphoma would be at an increased risk for radiation-associated cardiovascular disease if applying radiation to the chest. Using anthracyclines, such as doxorubicin, has demonstrated cardiotoxicity, and rituximab is associated with an increased risk of progressive multifocal leukoencephalopathy. In post-transplant individuals with CNS lymphoma, allograft failure is a risk, particularly if the immunosuppressant is reduced or halted to reconstitute immune function.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK545145/#article-27723.s1>

[CNS Lymphoma: Symptoms, Prognosis & Treatment](https://my.clevelandclinic.org/health/diseases/23474-cns-lymphoma)

# 

# 

# High-Grade B-Cell Lymphoma(Double Hit lymphoma)

**Definition and description**

High-grade B-cell lymphoma (HGBCL, previously known as double-hit lymphoma) is an aggressive type of B-cell non-Hodgkin lymphoma (NHL) characterized by rearrangements (parts of genes switch places within chromosomes) in two particular genes. One rearrangement involves the MYC gene, and the other involves the BCL2 gene or, less commonly, the BCL6 gene.

With respect to gene mutations, HGBCL shares many features with two other types of B-cell lymphomas—diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. In fact, about five percent of DLBCLs and about 32 to 78 percent of Burkitt lymphomas have rearrangements of the MYC and BCL2/BCL6 genes and are thus called HGBCL. However, research has shown that HGBCL differs in several important ways from the forms of DLBCL and Burkitt lymphoma that do not have dual gene rearrangements. For this reason, in 2016 the World Health Organization designated HGBCL as its own category of B-cell NHL.

Molecular tests allow doctors to check for gene rearrangements in chromosomes under a microscope that are used to confirm a diagnosis of HGBCL.

### B-cell lymphoma

B-cell lymphoma is a type of blood cancer in your lymphatic system. In B-cell lymphoma, abnormal lymphocytes (a type of white blood cell) multiply to form tumors. Your lymphatic system is a large network of organs, vessels and tissues, so B-cell lymphoma can develop in many places in your body and cause different symptoms.

B-cell lymphoma is a common type of non-Hodgkin lymphoma. There are many B-cell lymphoma types, but most cause the same symptoms: swollen lymph nodes, fatigue and drenching night sweats.

Often, treatment cures some types of B-cell lymphoma. And there are treatments that put the conditions into remission so you don’t have symptoms and tests don’t find signs of cancer. But the conditions can come back (recur).

#### Types of B-cell lymphoma

When your provider talks about your condition, they may use terms like “aggressive” or “indolent” to describe it:

* An aggressive type of B-cell lymphoma is one that can quickly spread (metastasize) from your lymphatic system to other organs or tissues in your body.
* An indolent type of the condition grows more slowly.

##### Aggressive (fast-growing) B-cell lymphoma

Aggressive B-cell lymphomas can develop in several areas of your body. Examples include:

* Burkitt lymphoma: This rare, fast-growing lymphoma may develop in your stomach and then spread to other organs.
* Diffuse large B-cell lymphoma (DLBCL): There are different forms of diffuse large B-cell lymphoma. It’s the most common type of non-Hodgkin lymphoma. DLBCL may start in your lymph nodes or a lymphoid organ like your thymus, spleen or tonsils.
* High-grade B-cell lymphoma (HGBCL): This type of B-cell lymphoma causes the same symptoms as DLBCL and Burkitt lymphoma. There are treatments that put the condition into remission, but it often comes back.

##### Indolent (slow-growing) B-cell lymphoma

You can have a type of indolent B-cell lymphoma for months and years before you develop symptoms. Common types include:

* Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): This type develops in your blood and bone marrow.
* Cutaneous B-cell lymphoma: This rare type starts in your skin.
* Follicular lymphoma: This is the second most common type of B-cell lymphoma. You may develop follicular lymphoma in your lymph nodes, bone marrow and other organs.
* Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia): This is a rare type of lymphoma that typically grows in your bone marrow, but may also develop in parts of your lymphatic system.
* Marginal zone lymphomas: There are different types of marginal zone lymphomas. Some develop in your stomach, lungs, skin, thyroid, salivary glands and tissues around your eyes.
* Mantle cell lymphoma: This B-cell lymphoma type often develops in your lymph nodes, bone marrow and spleen.

## Symptoms and Causes

You can have a type of B-cell lymphoma without having symptoms. For example, people with follicular lymphoma often receive a diagnosis while receiving treatment or tests for an unrelated condition. Symptoms that may be related to B-cell lymphoma include:

* Abdominal (belly) pain: Some types start in your belly, causing pain that doesn’t go away or gets worse.
* Drenching night sweats: This is sweating so much that your pajamas, sheets and blankets are soaking wet.
* Swollen lymph nodes: Painless lumps in your neck, armpit or groin are very common symptoms.
* Enlarged spleen or liver: B-cell lymphoma in your spleen or liver can make them get larger.
* Loss of appetite: Cancer in your spleen may make it press on your stomach, so you feel full even when you don’t eat very much.
* Persistent fatigue: Abnormal B cells in your bone marrow can affect red blood cell production and cause anemia (low red blood cell levels). Anemia can make you feel exhausted no matter how much rest you get.
* Pruritus (itchy skin): B-cell lymphoma in your liver may cause liver damage symptoms, including itchy skin.
* Rashes or skin lumps: Cutaneous B-cell lymphoma causes rashes, lumps and bumps on your skin. MALT lymphoma, a rare type of B-cell lymphoma, can cause skin changes, including lumps.
* Unexplained fever: A fever that stays above 100.4 degrees Fahrenheit (38.0 degrees Celsius) lasting more than two days or that comes back may be a B-cell lymphoma symptom.
* Unexplained weight loss: This is losing weight without trying to change what you eat and exercising.

B-cell lymphoma may cause symptoms that look and feel a lot like less serious medical issues. For example, swollen lymph nodes are a common B-cell lymphoma symptom. But they’re also a common symptom of colds and flu.

Having one or more of these symptoms doesn’t mean you have a type of B-cell lymphoma. But you should talk to a healthcare provider if you have symptoms that don’t go away or get worse.

### causes of B-cell lymphoma

Your B cells protect your body from invaders like bacteria, viruses and cancerous cells. Normally, your body produces new B cells as needed and the cells die once they’ve done their job.

In B-cell lymphoma, normal B cells change (mutate), turning into abnormal cells that multiply uncontrollably, don’t die and can spread from where they started to other areas of your body.

The condition typically happens because there are accidental (sporadic) changes in your B cells as they replicate themselves. Research suggests that sometimes, there’s a connection between B-cell lymphomas and the following issues:

* Autoimmune diseases, like rheumatoid arthritis, inflammatory bowel disease, Sjörgren’s syndrome and other related conditions.
* Being exposed to certain viruses, including HIV (human immunodeficiency virus), Epstein-Barr (mononucleosis) and Kaposi sarcoma human immunodeficiency virus.
* Having a family history of Hodgkin lymphoma.
* Having obesity.

## Diagnosis and Tests

A healthcare provider will ask about your symptoms and your medical history. They’ll do a physical examination that may focus on your lymph nodes, liver and spleen. They may refer you to a hematologist-oncologist, a provider who specializes in diagnosing and treating blood cancer. Your specialist may order blood tests, imaging tests and biopsies to diagnose your condition.

#### Blood tests

Blood tests for cancer give your healthcare provider a view of your overall health. Specific tests may include:

* Complete blood count (CBC) with differential: This test measures and counts your blood cells and platelets, including your B cells.
* Comprehensive metabolic panel (CMP): Your provider may order this test to check on substances in your blood that may be signs of B-cell lymphoma.
* Lactate dehydrogenase (LDH) levels: This test measures LDH levels. High LDH levels may be a sign of lymphoma or other diseases.

#### Imaging tests

Your provider may order the following imaging tests to look for signs of lymphoma in your lymph nodes, liver or spleen:

* CT scans.
* PET scans.
* Ultrasound.

#### Biopsy

A biopsy to obtain lymph node tissue is the only way your provider can confirm you have B-cell lymphoma. A medical pathologist will examine lymph node tissue samples to identify the lymphoma type. Biopsies may include:

* Excisional or incisional biopsy: In these procedures, a surgeon makes cuts in your body to remove lymph nodes for examination.
* Fine-needle aspiration (FNA): This procedure involves using a fine needle and a syringe to pull out cells for examination.
* Bone marrow biopsy: Providers use a special biopsy needle to remove a small piece of bone marrow for examination. Bone marrow biopsies are common tests to diagnose blood cancers like B-cell lymphoma.

## Management and Treatment

There’s no single treatment for B-cell lymphoma. If you have this condition, your treatment will depend on factors like the type, your overall health and if tests detect the condition before it spreads.

Your hematologist oncologist will recommend treatments that do the most to eliminate cancerous tumors while causing the fewest side effects. You may receive one or more of the following treatments:

* Chemotherapy.
* Immunotherapy.
* Radiation therapy.
* Targeted therapy. These include treatments such as monoclonal antibody therapy.
* Watchful waiting/active surveillance. If you have a type of slow-growing B-cell lymphoma and don’t have symptoms, your provider may do watchful waiting or active surveillance. Providers carefully monitor your overall health so they’re ready to start treatment as soon as you have symptoms.

#### Common treatment side effects

Each treatment may cause different side effects. And people often react differently to any given treatment. Your healthcare provider will select treatments that do the most to eliminate cancerous cells with the fewest side effects. Although cancer treatments are different, they do have some common side effects. Common side effects may include:

* Diarrhea.
* Fatigue.
* Nausea and vomiting.

Talk to your healthcare provider about each treatment option and potential side effects. Understanding how your treatment might affect you can help you feel more confident about managing side effects.

Regardless of the kind of treatment that you receive, also ask your provider about palliative care. Palliative care is a specialized treatment to help you manage B-cell lymphoma symptoms and treatment side effects.

## Outlook / Prognosis

There are many different types of B-cell lymphoma, so what you can expect depends on your situation and factors like the type of lymphoma, how well your body responded to treatment and your overall health. Your provider is your best resource for information on what to expect.

#### B-cell lymphoma survival rates

Survival rates vary widely depending on the type of lymphoma. For example, 64.6% of people with diffuse large B-cell lymphoma are alive five years after diagnosis. On the other hand, data show 90% of people with follicular lymphoma are alive five years after diagnosis.

If you’re receiving treatment for a type of B-cell lymphoma, ask your provider to explain survival rate information for your situation, including whether a survival rate can predict how long you’ll live. And try to keep in mind that any survival rate is an estimate based on the experiences of other people. What was true for them may not be true for you.

## Living With

B-cell lymphoma can be a life-changing diagnosis. You may feel overwhelmed as you try to take in information about your condition and treatment while trying to keep up with your daily life. Here are some suggestions that may help you:

* Have a plan for living with B-cell lymphoma. That plan might be lining up support during treatment, whether that’s arranging for special meals, transportation to appointments or someone to keep you company during treatment.
* Eat well. Treatment may affect your appetite. Consider working with a nutritionist so you fill your plate with food that you enjoy.
* Get your rest. Treatment can be exhausting. Plan to rest as much as possible, meaning rest when you need to, not just when you think you have time.
* Consider mental health support. Having cancer may make you feel anxious, angry, overwhelmed or depressed. Working with a mental health provider may help you understand and manage all those emotions.
* Find ways to relieve stress. Cancer is stressful. Consider activities such as meditation, relaxation exercises or deep breathing exercises.
* Reach out for support. Your healthcare provider can direct you to support groups and programs where you can express your feelings and concerns with people who understand what you’re going through.

### When should I see a doctor

You’ll see your hematologist-oncologist and other care team members throughout your treatment. They’ll manage your treatment and monitor your overall health. When you finish treatment, your provider may recommend a schedule of regular follow-up appointments so they can watch for signs that B-cell lymphoma is coming back.

## Epidemiology

### Occurrence in the United States

After a striking increase in incidence rates between 1970 and 1995 (which may in part have reflected improved diagnosis), the rates of new non-Hodgkin lymphoma (NHL) cases stabilized. From 2010-2019, rates of new cases fell on average 1.0% each year; and from 2011-2020, death rates fell on average 2.2% each year. The current US age-adjusted rate is 18.6 cases per 100,000 person-years for both sexes.The estimated rate for diffuse large B-cell lymphomas is approximately 4.68 cases per 100,000 person-years.

It is estimated that approximately 80,350 new cases of NHL will be diagnosed and 19,390 patients will die from NHL in 2025, despite currently available treatment.Lymphomas are a heterogeneous group of malignancies with diverse biology, clinical behavior, and prognosis.

In general, lymphomas can be divided into two groups, Hodgkin lymphoma (HL) and NHL. While infrequent, HL (8720 estimated new cases in 2025) is commonly diagnosed in younger patients and is curable with appropriate therapy in 85% of cases. In contrast, NHL is the seventh most common cancer in men and the sixth most common in women in the United States, accounting for 4% of all cancers, and the ninth leading cause of cancer deaths, accounting for 3% of cancer-related deaths.

Diagnosed cases of B-cell non-Hodgkin’s lymphoma (NHL) are set to increase by 15% in the next decade, according to a new analysis.

Analysts GlobalData say the complexity of the disease means health services need a “nuanced” understanding of its subtypes.

They studied the prevalence of the disease in seven wealthy countries: the USA, UK, Japan, France, Germany, Italy and Spain. The researchers say the number of annual diagnoses in these seven countries will increase from 200,844 in 2023 to 229,804 in 2033.

The number of patients living with the disease five years or more will increase from 634,000 to 714,000.

Senior epidemiologist Zachary Natale said: “Despite the progress that has been made, B-cell NHL remains a complex spectrum of malignant neoplasms, each of which exhibits idiosyncratic clinical manifestations and behaviours.

“Due to its heterogeneous impact on the clinical course of patients, it is imperative for healthcare workers, public health professionals, and researchers to develop a more nuanced understanding of B-cell NHL’s subtypes to best address them as respective diseases.”

## Diagnostic Considerations

Other problems to be considered include the following:

* Pseudolymphoma syndrome
* Carcinoma of unknown primary, especially in patients who present with significant lymphadenopathy in the mediastinum or abdomen.
* Mycobacterial infections, especially in patients with immune compromise; may manifest as fever, weight loss, and lymphadenopathy and, therefore, clinically mimic lymphoma.
* Fungal infections (eg, histoplasmosis, cryptococcosis in the acute phase) can similarly manifest as lymphadenopathy, fever, and (occasionally) weight loss, simulating lymphoma.

## Differential Diagnoses

* Hodgkin Lymphoma
* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Metastatic Cancer With Unknown Primary Site

## Other B-Cell Lymphomas

* Follicular Lymphoma (FL):
  + May have overlapping features with DLBCL, especially grade 3 FL which can resemble large B-cell lymphoma.
  + FL typically shows follicular architecture and expresses germinal center markers (CD10, BCL6).
* Burkitt Lymphoma (BL):
  + Characterized by monomorphic medium-sized cells, very high proliferation index (Ki-67 nearly 100%), and MYC rearrangement.
  + BL lacks large cells typical of DLBCL.
* Mantle Cell Lymphoma (MCL):
  + Usually expresses cyclin D1 and SOX11, with t(11;14) translocation.
  + Cells are typically medium-sized and may mimic DLBCL in blastoid variants.
* B-Lymphoblastic Lymphoma (B-LBL):
  + Immature B-cell neoplasm with TdT positivity, usually in children and young adults.
  + Needs to be distinguished from DLBCL due to different treatment.
* High-Grade B-Cell Lymphomas (HGBCL):
  + Includes “double-hit” and “triple-hit” lymphomas with rearrangements of MYC, BCL2, and/or BCL6.
  + Aggressive clinical behavior; immunophenotypic and cytogenetic studies required.
* Primary Mediastinal Large B-Cell Lymphoma (PMBCL):
  + Occurs in young adults, often females, with mediastinal mass.
  + Shares features with classical Hodgkin lymphoma (cHL) but distinct immunophenotype.

Hodgkin Lymphoma (HL)

* Classical Hodgkin lymphoma can mimic DLBCL, especially PMBCL and gray zone lymphomas.
* Reed-Sternberg cells in HL are CD30+, CD15+, and usually CD20-negative, contrasting with DLBCL which is CD20+.

Benign and Infectious Conditions

* Infectious Mononucleosis (EBV infection):
  + Can cause reactive lymphadenopathy with atypical lymphocytes mimicking lymphoma.
  + Clinical context and serology help differentiate.
* Benign Inoculation Lymphoreticulosis (Cat Scratch Disease):
  + Caused by *Bartonella henselae*, presents with localized lymphadenopathy.
* Metastatic Carcinoma:
  + Metastatic tumors to lymph nodes may mimic lymphoma clinically and radiologically.

Other Hematologic Malignancies

* T-Cell Lymphomas:
  + Some T-cell lymphomas may mimic B-cell lymphomas morphologically but differ immunophenotypically (CD3+, CD20−).

References

<https://emedicine.medscape.com/article/202677-differential?form=fpf>

<https://emedicine.medscape.com/article/202969-overview#a5>

[B-Cell Lymphoma: Symptoms, Treatment & Prognosis](https://my.clevelandclinic.org/health/diseases/22030-b-cell-lymphoma)

**GRAY ZONE LYMPHOMA**

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.

In this article, we’ll take a closer look at gray zone lymphoma, including its symptoms, diagnosis, treatment, and outlook.

## 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 of gray zone lymphoma and who’s at risk for it

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

## Diagnosis of gray zone lymphoma

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 in its 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

## What’s the outlook for someone who has 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.

Epidemiology

Reported as early as 1998, then with more frequency in 2005, GZL was subsequently recognized by the World Health Organization (WHO) in 2008. Due to its rarity, the incidence cannot be estimated definitively, however Qasrawi et al. estimated an incidence rate of 0.53 per million person-years based on confirmed GZL between 2005 and 2016 with age-adjusted incidence rates according to the US Standard Population in the year 2000 [17]. Furthermore, GZL is both a diagnostic and clinical dilemma faced by pathologists for its morphologic and phenotypic complexities and by oncologists for its aggressive clinical course and poor guideline defined treatment options [13,18]. One study recognized 68 cases of GZL across 15 North American Academic Centers and after central pathologic review by 5 hematopathologists, it was determined that only 26 cases were confirmed GZL [19].

Additionally in 2008, GZL had further been characterized as Mediastinal Gray Zone Lymphoma (MGZL) as well as Non-Mediastinal Gray Zone Lymphoma (NMGZL). MGZL is the name applied to gray zone lymphoma that has similar morphologic and phenotypic features to both classic Hodgkin's lymphoma and PMBL, and is found in the mediastinum. Typically, it affects young men and children with a male to female predominance of 1.4:1, which is notably different than PMBL and classic Hodgkin's lymphoma which have a female predominance. The mean age is 32–37 years which is also similar to the age of incidence in both CHL and PMBL [20,21].

NMGZL, which was previously thought to represent a heterogeneous subset of GZL, is no longer classified as a subset of GZL as of 2022. Cases with morphologic and immunophenotypic features similar to MGZL, but presenting outside and without involvement of the mediastinum should be classified as Diffuse Large B-cell Lymphoma not otherwise specified (DLBCL, NOS)

## Main Differential Diagnoses

| **Diagnosis** | **Key Distinguishing Features** |
| --- | --- |
| Classical Hodgkin Lymphoma (cHL) | Presence of Reed-Sternberg cells; strong CD30 and CD15 expression; weak or absent B-cell markers (CD20 usually negative or weak); OCT-2 and BOB.1 negative or weak; usually CD45 negative. |
| Primary Mediastinal Large B-Cell Lymphoma (PMBCL) | Strong expression of B-cell markers (CD20, CD79a, PAX5), OCT-2 and BOB.1 positive; CD30 positive but weaker and more heterogeneous than cHL; absence of CD15; typically lacks Reed-Sternberg cells. |
| Diffuse Large B-Cell Lymphoma (DLBCL), Not Otherwise Specified | Lacks the characteristic mediastinal presentation and overlapping immunophenotype; usually strong B-cell marker expression and absence of cHL features. |
| EBV-Positive Lymphomas | EBV+ cHL and EBV+ DLBCL need to be considered, especially in EBV+ GZL cases. EBV status assessed by EBER in situ hybridization. |
| Other Mediastinal Masses | Thymoma, germ cell tumors, other lymphomas (e.g., nodular lymphocyte-predominant Hodgkin lymphoma) may be considered clinically but distinguished histologically. |

REFERENCES

<https://pmc.ncbi.nlm.nih.gov/articles/PMC10242558/>

### Multiple Myeloma

**Definition and description**

Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Healthy plasma cells help fight infections by making proteins called antibodies. Antibodies find and attack germs.

* In multiple myeloma, cancerous plasma cells build up in bone marrow. The bone marrow is the soft matter inside bones where blood cells are made. In the bone marrow, the cancer cells crowd out healthy blood cells. Rather than make helpful antibodies, the cancer cells make proteins that don't work right. This leads to complications of multiple myeloma.
* Multiple myeloma treatment isn't always needed right away. If the multiple myeloma is slow growing and isn't causing symptoms, close watching might be the first step. For people with multiple myeloma who need treatment, there are a number of ways to help control the disease.

## How does multiple myeloma start?

When plasma cells become cancerous and grow out of control, this is generally called multiple myeloma.

Plasma cells are a type of white blood cell found in your bone marrow. They are one of several types of cells in your immune system that work together to fight infections and other diseases.

Normal plasma cells fight off infections by making proteins called antibodies (also called immunoglobulins) which help your body attack and kill germs. But sometimes, plasma cells become cancerous and grow out of control.

When this happens, the plasma cells make an abnormal antibody. This antibody is known by different names, including monoclonal immunoglobulin, monoclonal protein (M-protein), M-spike, or paraprotein.

### Plasma cell disorders

Plasma cells sometimes grow in other, unusual ways that don’t meet the criteria to be called active multiple myeloma. These conditions are described in Other Plasma Cell Disorders (below).

## Multiple myeloma features

Multiple myeloma can affect the blood, bones, and other organs, which can lead to problems in different parts of the body.

### Low blood counts

In multiple myeloma, the overgrowth of plasma cells in the bone marrow can crowd out normal blood-forming cells, leading to low blood counts.

* Anemia (a shortage of red blood cells) can cause a person to feel weak, fatigued (tired), or short of breath.
* Thrombocytopenia (a shortage of platelets in the blood) can lead to an increased risk of bleeding and bruising.
* Leukopenia (a shortage of normal white blood cells) can increase the risk of infections.

### Bone and calcium problems

Myeloma cells can also interfere with cells that help keep bones strong. Two kinds of bone cells constantly work together to keep bones healthy and strong:

* Osteoclasts break down old bones.
* Osteoblasts lay down new bones.

Myeloma cells make a substance that tells the osteoclasts to speed up dissolving the bone. So old bone is broken down without new bone to replace it, making the bones weak and easy to break. Fractured bones are a major problem in people with myeloma.

### Infections

Abnormal plasma cells can’t protect your body from infections. Normal plasma cells make antibodies that attack germs. But in multiple myeloma, the myeloma cells crowd out the normal plasma cells, so antibodies that fight infections can’t be made.

### Kidney problems

The antibodies made by myeloma cells can harm your kidneys, leading to kidney damage or even kidney failure.

## Other plasma cell disorders

A few plasma cell disorders involve unusual plasma cell growth but don’t meet the criteria for active multiple myeloma. These include:

* Monoclonal gammopathy of undetermined significance (MGUS)
* Solitary plasmacytoma
* Smoldering multiple myeloma (SMM)
* Light chain amyloidosis

### Monoclonal gammopathy of undetermined significance (MGUS)

In monoclonal gammopathy of undetermined significance (MGUS), abnormal plasma cells make many copies of the same antibody (called a monoclonal protein). However, these plasma cells don’t form an actual tumor or mass, and they don’t cause the other health problems that can be seen in multiple myeloma.

MGUS doesn’t damage bones or cause high calcium levels, kidney problems, or low blood counts. It’s most often found when a routine blood test finds a high level of protein in the blood and further testing shows the protein is a monoclonal antibody.

In MGUS, the number of plasma cells may be increased, but they still make up less than 10% of the cells in the bone marrow.

MGUS is not considered cancer, but some people with MGUS will eventually develop a cancer such as multiple myeloma or lymphoma. They might also develop amyloidosis, a condition linked with blood cancers (see below). Each year, about 1% of people with MGUS develop one of these diseases. The risk is greater in people whose monoclonal protein levels are particularly high.

People with MGUS don’t need treatment, but they are watched closely to see if they get a disease that *does* need to be treated, such as multiple myeloma.

**Causes of MGUS**

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 of MGUS**

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 of MGUS**

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 of MGUS

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 hip bones for study. This usually is only for those at risk of getting a more serious disease or other problems linked to MGUS.

**Treatment of MGUS**

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 increases bone mass. Examples include alendronate (Fosamax), risedronate (Actonel, Atelvia), ibandronate and zoledronic acid (Reclast, Zometa).

### Solitary plasmacytoma

A plasmacytoma is a type of plasma cell tumor. Rather than many tumors in different locations as in multiple myeloma, there is only one tumor, hence the name solitary plasmacytoma.

A solitary plasmacytoma often develops in a bone. When a plasmacytoma starts in other body tissues (such as the lungs or other organs), it is called a solitary extramedullary (or extraosseous) plasmacytoma.

Solitary plasmacytomas can usually be treated with radiation therapy and/or surgery. As long as no other plasmacytomas are found later on, the person’s outlook is usually excellent. However, people with a solitary plasmacytoma might develop multiple myeloma later, so they need to be watched closely for signs of this disease.

### Smoldering multiple myeloma ﻿(SMM)

Smoldering multiple myeloma (SMM), also known as asymptomatic myeloma, is an early form of myeloma that is not causing any symptoms. People with smoldering myeloma have some signs of multiple myeloma, such as any of the following:

* A higher-than-normal amount of plasma cells in the bone marrow
* A high level of monoclonal immunoglobulin (monoclonal protein) in the blood
* A high level of light chains (also called Bence Jones protein) in the urine

However, they have normal blood counts, normal calcium levels, normal kidney function, no bone or organ damage, and no signs of amyloidosis (see below).

Most people with smoldering multiple myeloma don’t need treatment right away, because the disease can take anywhere from many months to years to become active (symptomatic) myeloma.

Some people may have very slow disease that never becomes active myeloma, but for others the risk is higher, so earlier treatment might be helpful.

### Light chain amyloidosis

Light chain amyloidosis (also known as AL amyloidosis or primary amyloidosis) is also a disorder of abnormal plasma cell growth, but with lower amounts of abnormal plasma cells in the bone marrow compared to multiple myeloma.

Monoclonal proteins (antibodies) are made up of joined protein chains – 2 short light chains and 2 longer, heavy chains. In light chain amyloidosis, abnormal plasma cells make too many light chains. The light chains build up in tissues as an abnormal protein known as amyloid.

The buildup of amyloid in certain organs can enlarge them and affect the way they work. For example:

* When amyloid builds up in the heart, it can cause an irregular heartbeat and can make the heart larger and weaker. A weak heart can lead to a condition called congestive heart failure, with symptoms like shortness of breath and swelling in the legs.
* Amyloid in the kidneys can affect how well they work. This may not cause symptoms early on, but the poor kidney function may be seen on blood tests. If it gets bad enough, it can lead to kidney failure.

Light chain amyloidosis is only one of the diseases where amyloid builds up and causes problems. Amyloidosis can also be caused by a genetic (hereditary) disease called familial amyloidosis. Long-standing (chronic) infection and/or inflammation can also cause amyloidosis. This is known as secondary or AA amyloidosis.

### Waldenstrom macroglobulinemia (WM)

The cancer cells in people with WM are similar to those in multiple myeloma and non-Hodgkin lymphoma (NHL). Multiple myeloma is considered a cancer of plasma cells, and non-Hodgkin lymphoma is a cancer of lymphocytes. WM cells have features of both plasma cells and lymphocytes*.*

Lymphocytes are one of the main types of white blood cells in the immune system. They include T cells and B cells, and they are in many areas of your body, including your lymph nodes, bone marrow, intestines, and bloodstream. When B cells respond to an infection, they mature and change into plasma cells.

Even though WM is sometimes grouped with other plasma cell disorders, it is considered a type of NHL.

Waldenstrom macroglobulinemia grows slowly. It might not cause symptoms for years.

When they happen, Waldenstrom macroglobulinemia symptoms may include:

* Fatigue.
* Fever.
* Weight loss.
* Night sweats.
* Numbness in the hands or feet.
* Swollen lymph nodes.
* A feeling of pain or fullness under the ribs on your left side, which may be caused by an enlarged spleen.
* Easy bruising.
* Bleeding nose or gums.
* Headache.
* Shortness of breath.
* Changes in vision.
* Confusion.

**Causes of waldenstrom macroglobulinemia**

Cancer happens when cells develop changes in their DNA. A cell's DNA holds the instructions that tell a cell what to do. The changes tell the cells to multiply quickly. The cells continue living when healthy cells would die as part of their natural lifecycle.

In Waldenstrom macroglobulinemia, the changes happen in the white blood cells. The changes turn some of the white blood cells into cancer cells. It's not clear what causes the changes.

The cancer cells can build up in the spongy material inside the bones where blood cells are made. This material is called bone marrow. The cancer cells crowd healthy blood cells out of the bone marrow. The cancer cells also may build up in the lymph nodes and the spleen.

Waldenstrom macroglobulinemia cells make a protein that the body can't use. The protein is immunoglobulin M, which is also called IgM. IgM can build up in the blood. This may reduce blood flow in the body and cause other problems.

**Risk factors OF WALDENSTROM MACROGLOBULINEMIA**

Factors that can increase the risk of Waldenstrom macroglobulinemia include:

* **Being older.** Waldenstrom macroglobulinemia can occur at any age, but it's most often found in adults 70 and older.
* **Being male.** Males are more likely to have Waldenstrom macroglobulinemia.
* **Being white.** White people are more likely to develop the disease, compared with people of other races.
* **Having a family history of lymphoma.** Having a relative who has Waldenstrom macroglobulinemia or another type of B-cell lymphoma might increase your risk.

## Diagnosis and test of waldenstrom macroglobulinemia

A physical exam, medical history and the following tests are used to diagnose Waldenstrom macroglobulinemia:

* **Blood tests.** Blood tests can show if there are too few healthy blood cells. Also, blood tests detect a protein made by the cancer cells. This protein is immunoglobulin M, which is also called IgM.  
  Blood tests also can show how well organs are working. Results can show whether the IgM proteins are harming organs, such as the kidneys and the liver.
* **Collecting a sample of bone marrow for testing.** During a bone marrow biopsy, a needle is used to take some bone marrow from the hipbone. The sample goes to a lab where it is tested for cancer cells. If there are cancer cells, more tests can give more information about the cells.
* **Imaging tests.** Imaging tests can help show whether cancer has spread to other areas of the body. Imaging tests might include CT scans or positron emission tomography scans, which are also called PET scans.

**Treatment of waldenstrom macroglobulinemia**

Treatment options for Waldenstrom macroglobulinemia may include:

* **Watchful waiting.** If IgM proteins are in the blood, but there are no symptoms, treatment might not be needed right away. Instead, you might have blood tests every few months to monitor your condition. Doctors sometimes call this watchful waiting. There might be no need for treatment for years.
* **Plasma exchange.** Plasma exchange, also known as plasmapheresis, removes IgM proteins from the blood. It replaces them with healthy blood plasma. Plasma exchange can relieve symptoms caused by having too many IgM proteins in the blood.
* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells throughout the body. Chemotherapy used alone or with other medicines might be the first treatment for people who have symptoms of Waldenstrom macroglobulinemia. Also, high-dose chemotherapy can stop bone marrow from making cells and may be used to prepare for a bone marrow transplant.
* **Targeted therapy.** Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy medicines might be used with other treatments, such as chemotherapy or immunotherapy.
* **Immunotherapy.** Immunotherapy is a treatment with medicine that helps your body's immune system to kill cancer cells. Your immune system fights off diseases by attacking germs and other cells that shouldn't be in your body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.
* **Bone marrow transplant.** In select instances, a bone marrow transplant, also known as a stem cell transplant, may be a treatment for Waldenstrom macroglobulinemia. During this procedure, high doses of chemotherapy wipe out the bone marrow. Healthy blood stem cells go into the body to rebuild healthy bone marrow.
* **Supportive care.** Supportive care, which is also called palliative care, focuses on relieving pain and other symptoms of serious illness. This extra layer of care can support you as you undergo other treatments, such as chemotherapy.

**Causes of myeloma**

It's not clear what causes myeloma.

Multiple myeloma begins with one plasma cell in the bone marrow. The bone marrow is the soft matter inside bones where blood cells are made. Something happens that turns the plasma cell into a cancerous myeloma cell. The myeloma cell begins making a lot more myeloma cells quickly.

Healthy cells grow at a set pace and die at a set time. Cancer cells don't follow these rules. They make a lot of extra cells. The cells continue living when healthy cells die. In myeloma, the cancer cells build up in the bone marrow and crowd out the healthy blood cells. This leads to tiredness and not being able to fight infections.

The myeloma cells continue trying to make antibodies, as healthy plasma cells do. But the body can't use these antibodies, called monoclonal proteins or M proteins. Instead, the M proteins build up in the body and cause problems, such as damage to the kidneys. Myeloma cells can damage bones and increase the risk of broken bones.

### A connection with MGUS

Multiple myeloma starts as a condition called monoclonal gammopathy of undetermined significance, also called MGUS. In MGUS, the level of M proteins in the blood is low. The M proteins don't cause damage in the body.

**Symptoms of multiple myeloma**

Early in multiple myeloma, there might be no symptoms. When signs and symptoms happen, they can include:

* Bone pain, especially in the spine, chest or hips.
* Nausea.
* Constipation.
* Loss of appetite.
* Mental fogginess or confusion.
* Tiredness.
* Infections.
* Weight loss.
* Weakness.
* Thirst.
* Needing to urinate often.

### 

### When to see a doctor

Make an appointment with a doctor or other health care professional if you have symptoms that worry you.

### Stages

The results of your tests help your healthcare team decide your myeloma's stage. In multiple myeloma, the stages range from 1 to 3. The stage tells your health care team how quickly your myeloma is growing. A stage 1 multiple myeloma is growing slowly. As the stages get higher, the myeloma becomes more aggressive. A stage 3 multiple myeloma is getting worse quickly.

Multiple myeloma can also be given a risk level. This is another way to say how aggressive the disease is.

Your health care team uses the multiple myeloma stage and risk level to understand your prognosis and plan your treatment.

## Drug therapy used to treat multiple myeloma

A single drug might sometimes be used to treat multiple myeloma. But most often, 2 to 4 different kinds of drugs are combined because this tends to work better. The choice of which drugs to use depends on many factors, including:

* T﻿he traits of the myeloma (including if it's considered high risk or standard risk)
* Your age, kidney function, and overall health
* If you might get a stem cell transplant as part of your treatment﻿

The rest of this page gives information about the medicines used to treat multiple myeloma, including their possible side effects. To learn more about how some of these medicines might be combined,

**Immunomodulatory drugs (IMiDs)**

Immunomodulatory drugs (IMiDs) affect the immune system, although exactly how they do this isn’t entirely clear. These drugs are often helpful in treating multiple myeloma.

IMiDs are taken daily as pills, with breaks from treatment on certain days each month. Because these drugs can increase the risk of serious blood clots, they are often given along with aspirin or a blood thinner.

IMiDs might cause severe birth defects when taken during pregnancy, so you can only get them through a special program run by the drug company that makes them.

### Thalidomide (Thalomid)

Thalidomide was the first IMiD used to treat multiple myeloma.

Side effects of thalidomide can include drowsiness, fatigue, severe constipation, and painful nerve damage (neuropathy). The neuropathy can be severe, and it might not go away after the drug is stopped. There is also an increased risk of serious blood clots that start in the leg and can travel to the lungs.

### Lenalidomide (Revlimid)

Lenalidomide is similar to thalidomide, although it tends to have less severe side effects. This is often the first IMiD used in treating multiple myeloma.

The most common side effects of lenalidomide are low blood platelet counts (thrombocytopenia), low white blood cell counts, and diarrhea. It can also cause painful nerve damage. The risk of blood clots is not as high as with thalidomide, but it is still increased.

### Pomalidomide (Pomalyst)

Pomalidomide can also be used to treat multiple myeloma, most often after other treatments have been tried.

Some common side effects of pomalidomide include low red blood cell counts (anemia), low white blood cell counts, and fatigue. The risk of nerve damage is not as high as with the other IMiDs. There is also an increased risk of blood clots.

## Corticosteroids (steroids)

Corticosteroids, such as dexamethasone and prednisone, are an important part of the treatment of multiple myeloma. They can be used alone or combined with other drugs as a part of treatment.

Corticosteroids can also be used to help reduce the nausea and vomiting that chemo might cause.

### Side effects of corticosteroids

Common side effects of corticosteroids can include:

* High blood sugar
* Increased appetite and weight gain
* Problems sleeping
* Changes in mood, such as becoming irritable or “hyper”

When corticosteroids are used for a long time, they can also suppress your immune system, which increases the risk of serious infections. Steroids can also weaken your bones.

Most of these side effects go away over time after the drug is stopped.

## Proteasome inhibitors

Proteasome inhibitors stop enzyme complexes (proteasomes) in your cells from breaking down certain proteins that are important for controlling cell division. These drugs affect tumor cells more than normal cells.

### Bortezomib (Velcade)

Bortezomib was the first proteasome inhibitor to be approved, and it’s often used to treat multiple myeloma. It may be especially helpful in treating people with kidney problems.

It’s injected into a vein (IV) or under the skin, once or twice a week.

Common side effects of bortezomib include:

* Nausea and vomiting
* Tiredness
* Diarrhea
* Constipation
* Fever
* Loss of appetite
* Lowered blood counts, especially platelet counts (which can cause easier bruising and bleeding) and white blood cell counts (which can increase the risk of serious infection)

Bortezomib can also cause nerve damage (peripheral neuropathy) that can lead to problems with numbness, tingling, or even pain in the hands and feet. The risk of nerve damage is less when the drug is given weekly under the skin.

Some people get shingles (herpes zoster) while taking this drug. To help prevent this, your doctor may have you take an antiviral medicine (like acyclovir) while you take bortezomib.

### Carfilzomib (Kyprolis)

Carfilzomib is a proteasome inhibitor that can be used to treat multiple myeloma. It’s given as an injection into a vein (IV), typically once or twice a week. To help prevent problems like allergic reactions during the infusion, the steroid drug dexamethasone is often given before each dose in the first cycle.

Common side effects of carfilzomib include:

* Tiredness
* Nausea and vomiting
* Diarrhea
* Shortness of breath
* Fever
* Low blood counts, including platelet counts (which can cause easier bruising and bleeding) and red blood cell counts (which can lead to tiredness and shortness of breath)

People on this drug can also have more serious problems, such as pneumonia, heart problems, and kidney or liver failure.

### Ixazomib (Ninlaro)

Ixazomib is a proteasome inhibitor that is taken by mouth as a capsule, typically once a week for 3 weeks, followed by a week off. This drug is usually given after other drugs have been tried.

Common side effects of ixazomib include:

* Nausea and vomiting
* Diarrhea
* Constipation
* Swelling in the hands or feet
* Back pain
* Lowered blood platelet counts (which can cause easier bruising and bleeding)

This drug can also cause nerve damage (peripheral neuropathy) that can lead to problems with numbness, tingling, or even pain in the hands and feet.

## Monoclonal antibodies

Antibodies are proteins made by the body’s immune system to help fight infections. Man Made versions (monoclonal antibodies) can be designed to attack a specific target, such as proteins on the surface of myeloma cells.

### Antibodies against CD38

The CD38 protein is found on myeloma cells. Monoclonal antibodies that target this protein seem to work both by killing the cancer cells directly and by helping the immune system attack them.

#### Daratumumab (Darzalex and Darzalex Faspro)

Daratumumab is a monoclonal antibody that attaches to the CD38 protein. This drug is used mainly in combination with other types of drugs, although it can also be used by itself in people who have already had other treatments for myeloma.

This drug can be given as an infusion into a vein (IV). A newer form of the drug, known as daratumumab and hyaluronidase (Darzalex Faspro), can be given as a subcutaneous injection (under the skin). This is typically done in the belly area over a few minutes.

Either form of this drug can cause a reaction in some people, either while it’s being given or within several hours afterward. These reactions can sometimes be severe. Symptoms can include coughing, wheezing, trouble breathing, tightness in the throat, a runny or stuffy nose, feeling dizzy or lightheaded, headache, rash, and nausea.

Other side effects can include fatigue, nausea, back pain, fever, and cough. This drug can also lower blood cell counts, which can increase the risk of infections and bleeding or bruising. Darzalex Faspro can also cause reactions at the injection site, such as swelling, itching, and redness.

#### Isatuximab (Sarclisa)

Isatuximab is another monoclonal antibody that attaches to the CD38 protein on myeloma cells.

This drug is used along with other types of myeloma drugs, either after other treatments have been tried or as part of the first treatment for some people. It’s given as an infusion into a vein (IV), typically once every 1, 2, or 4 weeks.

Isatuximab can cause a reaction in some people, while it’s being given or within a few hours afterward. These reactions can sometimes be severe. Symptoms can include coughing, wheezing, trouble breathing, tightness in the throat, chills, feeling dizzy or lightheaded, headache, rash, and nausea.

The most common side effects of isatuximab include respiratory infections (such as colds or pneumonia) and diarrhea. This drug can also lower blood cell counts:

* Having too few white blood cells can increase your risk for infections.
* Having too few red blood cells (anemia) can make you feel tired and weak.
* Having too few blood platelets can increase your risk of bleeding and bruising easily.

This drug might also increase your risk of developing a second cancer.

### Antibodies against SLAMF7

SLAMF7 is another protein found on myeloma cells. Antibodies that target this protein can help the immune system attack the cancer cells.

#### Elotuzumab (Empliciti)

Elotuzumab is a monoclonal antibody that attaches to the SLAMF7 protein. This drug is used in combination with other medicines, mainly in people who have already had other treatments for their myeloma. It’s given as an infusion into a vein (IV).

This drug can cause a reaction in some people, while it’s being given or within several hours afterward. These reactions can sometimes be severe. Symptoms can include fever, chills, feeling dizzy or lightheaded, rash, wheezing, trouble breathing, tightness in the throat, or a runny or stuffy nose.

Other common side effects of Elotuzumab include fatigue, fever, loss of appetite, diarrhea, constipation, cough, upper respiratory tract infections, pneumonia, and nerve damage resulting in weakness or numbness in the hands and feet (peripheral neuropathy).

## T-cell engagers (TCEs)

Some newer man made antibodies are designed to attach to two different targets. These are known as bispecific antibodies.

An example is T-cell engagers (TCEs). Once in the body, one part of these antibodies attaches to the CD3 protein on immune cells called *T cells*. Another part attaches to a specific protein on myeloma cells. This brings the two cells together, which helps the immune system attack the myeloma cells.

These medicines can be an option to treat multiple myeloma, typically after other types of drugs have been tried.

### Teclistamab (Tecvayli)

Teclistamab attaches to the BCMA protein on myeloma cells. This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then once a week. After several months, it can also be given once every 2 weeks.

### Elrenatamab (Eltex Fio)

Elrenatamab also attaches to the BCMA protein on myeloma cells. This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then once a week for several months, and then once every 2 weeks.

### Talquetamab (Talvey)

Talquetamab attaches to the GPRC5D protein on myeloma cells (and some other cells). This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then either once a week or once every other week.

### Side effects of TCEs

TCEs can cause serious side effects when you first get them. Because of this, you will be starting on a low dose. You might be given other medicines to help lower your risk of side effects, and you might need to stay in the hospital for a day or two after the first few doses.

Common side effects of TCEs include:

* Fever
* Feeling very tired
* Headache
* Nausea
* Diarrhea
* Muscle and joint pain
* Respiratory infections (including pneumonia)
* Low blood cell counts
* Skin rash
* Liver problems﻿

More serious side effects of TCEs can include:

* Cytokine release syndrome (CRS): A serious side effect in which T cells in the body release chemicals (cytokines) that ramp up the immune system. This happens most often within the first day after treatment, and it can sometimes be life-threatening. Symptoms can include high fever and chills, feeling dizzy or lightheaded, trouble breathing, low blood pressure, headache, and a very fast heartbeat.
* Nervous system problems: These drugs might affect the nervous system, which could lead to symptoms such as headaches, numbness or tingling in your hands or feet, feeling dizzy or confused, having trouble speaking or understanding things, memory loss, abnormal sleep patterns, tremors, or seizures.
* Infections: These drugs can increase the risk of infection, both in the short term and the long term. Your doctor may recommend medicines to help prevent or treat a possible infection before you have any symptoms.

Your health care team will watch you closely for possible signs of these problems, especially during and after the first few treatments. Be sure to contact them right away if you have any of the symptoms above.

These drugs might also cause other problems. Ask your health care team what you should look out for.

## Traditional chemotherapy

Chemotherapy (chemo) is the use of certain kinds of drugs that destroy or control the growth of cancer cells. These drugs can be taken by mouth or given in a vein or a muscle. They enter the bloodstream and reach almost all areas of the body.

At one time, chemo was often part of the main treatment for multiple myeloma. As newer types of drugs have become available in recent years, chemo has become less important in treating myeloma, although it still might be used in some situations.

Chemo drugs that can be used to treat multiple myeloma include:

* Cyclophosphamide
* Etoposide (VP-16)
* Doxorubicin (Adriamycin)
* Liposomal doxorubicin
* Melphalan
* Bendamustine
* Cisplatin
* Carmustine

Often, one of these drugs is combined with other types of drugs like corticosteroids and immunomodulating drugs (IMiDs, see above). If a stem cell transplant is planned as part of treatment, most doctors avoid using certain chemo drugs, like melphalan, that can damage bone marrow.

### Chemo side effects

Chemo drugs kill cancer cells but also can damage normal cells, which can lead to side effects. These side effects depend on the type and dose of drugs given and how long they are taken. Common side effects of chemo include:

* Hair loss
* Mouth sores
* Loss of appetite
* Nausea and vomiting
* Diarrhea or constipation

Chemotherapy often leads to low blood counts, which can cause:

* An increased risk of serious infection (from having too few white blood cells)
* Easy bruising or bleeding (from having too few blood platelets )
* Feeling tired or short of breath (from having too few red blood cells)

Most side effects go away after treatment is finished.

If you have side effects, your cancer care team can suggest steps to ease them. For example, drugs can be given along with the chemo to prevent or reduce nausea and vomiting.

Along with these short-term side effects, some chemo drugs can cause long-term damage to certain organs such as the heart or kidneys. The possible risks of these drugs are carefully balanced against their benefits, and the function of these organs is carefully monitored during treatment.

## Nuclear export inhibitor

The nucleus of a cell holds most of the cell’s genetic material (DNA) needed to make the proteins the cell uses to function and stay alive. A protein called XPO1 helps carry other proteins from the nucleus to other parts of the cell.

### Selinexor (Xpovio)

Selinexor is a drug known as a nuclear export inhibitor. It works by blocking the XPO1 protein. When the myeloma cell cannot transport proteins from its nucleus, the cell dies.

This drug is a pill that can be taken weekly or on the first and third day of each week. It can be used, along with the steroid dexamethasone:

* For people whose myeloma is no longer responding to other myeloma drugs, OR
* Along with bortezomib for people whose myeloma has grown on at least one other drug therapy

Common side effects of selinexor include low platelet counts, low white blood cell counts, diarrhea, nausea, vomiting, not feeling hungry, weight loss, low blood sodium levels, and infections like bronchitis or pneumonia.

## Bisphosphonates and other drugs for bone disease

Myeloma cells can weaken and even break bones. Drugs that affect bone cells can help bones stay strong by slowing down this process. They can also help reduce pain in the weakened bone(s). Sometimes, pain medicines such as NSAIDs or opioids will be given along with one of these medicines to help control or lessen pain from the bones.

The drugs used most often for treating bone problems in people with myeloma are the bisphosphonates pamidronate (Aredia) and zoledronic acid (Zometa) and the drug denosumab (Xgeva and other brand names).

Treatment with one of these drugs helps prevent further bone damage and events related to weakened bones such as fractures, hypercalcemia (high blood calcium levels), and spinal cord compression in people with multiple myeloma.

### How bone medicines are given

These drugs are given intravenously (IV or into a vein) or subcutaneously (under the skin). Most people are treated once a month at first, but they may eventually be treated less often if they are doing well.

Treatment with one of these drugs is often given for up to 2 years, after which the need for continuing it is reassessed. If the myeloma comes back and new bone problems develop, treatment with a bone-disease drug is usually started again.

Talk with your cancer care team to learn more about stopping and restarting treatment with these medicines.

### Common side effects of bone medicines

* Side effects of bisphosphonates can include flu-like symptoms and bone or joint pain. These drugs (especially zoledronic acid) can also cause kidney problems, so people with poor kidney function might not be able to take them.
* Common side effects of denosumab can include nausea, diarrhea, and feeling weak or tired. This drug can be given safely to people with kidney problems.

### Osteonecrosis of the jaw (ONJ)

All of these bone medicines can have a rare but serious side effect called osteonecrosis of the jaw (ONJ), in which part of the jaw bone loses its blood supply and dies. This can lead to an open sore that doesn’t heal. It can also lead to tooth loss in that area. The jaw bone can also become infected.

Doctors aren’t sure why this happens or how best to prevent it, but having jaw surgery or having a tooth removed can sometimes trigger this problem, so it's important to avoid these procedures while you are taking any of these medicines.

One way to avoid these procedures is to maintain good oral hygiene by flossing, brushing, making sure that dentures fit properly, and having regular dental checkups. Any tooth or gum infections should be treated right away.

Dental fillings, root canal procedures, and tooth crowns do not seem to lead to ONJ. If ONJ does happen, the doctor will stop the bone medicine.

Your doctor might recommend that you have a dental checkup before starting one of these medicines. They might also recommend taking calcium and vitamin D supplements while taking the medicine to help your body build bone.

### Treating complications

## Treatment might include treating complications of multiple myeloma. For example:

## Bone pain. Pain medications, radiation therapy and surgery may help control bone pain.

## Kidney damage. People with severe kidney damage may need dialysis.

## Infections. Vaccines can help prevent infections, such as the flu and pneumonia.

## Bone loss. Bone-building medicines might help prevent bone loss.

## Anemia. Medicines can increase the number of red blood cells in the blood. This can help relieve ongoing anemia.

# Can Multiple Myeloma Be Prevented?

## There is no sure way to prevent multiple myeloma. But there might be things you can do to help lower your risk.

## Lowering your risk of multiple myeloma

## Most of the risk factors for multiple myeloma, like your age and family history, can’t be changed or controlled. But there are things you can do that might help lower your risk:

## Get to and stay at a healthy weight.

## If possible, avoid radiation and chemicals that might raise multiple myeloma risk.

## MGUS and the risk of myeloma

## Some people are known to be at increased risk of myeloma. This includes people with monoclonal gammopathy of undetermined significance (MGUS). At this time, there is no known way to prevent people with MGUS from getting multiple myeloma, but this is an active area of research.

## Epidemiology

MM accounts for 10% of all hematologic cancers. The American Cancer Society estimates that in the United States, approximately 36,110 new cases of MM (20,030 in men and 16,080 in women) will be diagnosed in 2025.The lifetime risk of getting MM is approximately 1 in 108 for men and 1 in 133 for women (overall, 0.8%).Approximately 12,030 deaths from MM (6540 in men and 5490 in women) are expected to occur in the US in 2025.Rates for new MM cases rose slightly over the last decade, from 7.0 per 100,000 persons in 2011 to 7.1 per 100,000 persons in 2021, while death rates declined slightly, from 3.4 to 2.8 per 100,000 from 2012 to 2022.

In the US, the annual incidence of MM per 100,000 persons is 8.1 cases in White men, 5.1 cases in White women, 17.1 cases in Black men, and 13.0 cases in Black women. For Hispanics, the rates are 7.9 in men and 5.8 in women. Rates are lowest for Asians/Pacific Islanders, at 5.1 in men and 3.3 in women.According to a study of the ethnic disparities among patients with MM, Hispanics had the youngest median age at diagnosis (65 years) and Whites had the oldest (71 years).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for many of the vague symptoms accompanying multiple myeloma is broad. However, several entities must be considered and ruled out before diagnosis and treatment. Following is a list of important diseases to consider and how to differentiate these from multiple myeloma:

**Monoclonal Gammopathy of Undetermined Significance (MGUS)**

* Serum monoclonal protein less than 3 g/dl
* Clonal bone marrow plasma cells less than 10%
* No end-organ damage

**Smoldering Multiple Myeloma**

* Monoclonal protein is greater than or equal to 3 g/dl
* Clonal bone marrow plasma cells between 10% to 59%
* No end-organ damage

**Solitary Plasmacytoma**

* Solitary lesion made up of clonal plasma cells
* Normal bone marrow
* Negative imaging outside of the single lesion
* No end-organ damage

**Waldenstrom Macroglobulinemia**

* Lymphoplasmacytic lymphoma noted in the bone marrow
* The type of M protein is IgM which is very unusual in MM.
* Presence of MYD88 L265P
* Symptoms include hyperviscosity, peripheral neuropathy, anemia, lymphadenopathy, and hepatosplenomegaly

**AL Amyloidosis**

* Caused by deposition of amyloid fibrils or non-fibrillar material resulting in heart failure, hepatomegaly, and/or nephrotic syndrome
* Less than 20% plasma cells in the bone marrow and lack of lytic lesions
* Congo-red staining on bone marrow or affected tissue

## References

[↑](https://www.wikidoc.org/index.php/Multiple_myeloma_differential_diagnosis#cite_ref-seer_1-0) ["Myeloma - SEER Stat Fact Sheets"](http://seer.cancer.gov/statfacts/html/mulmy.html). Retrieved 17 February 2014.

<https://emedicine.medscape.com/article/204369-differential?form=fpf>

https://www.ncbi.nlm.nih.gov/books/NBK534764/#article-25360.s10

[↑](https://www.wikidoc.org/index.php/Multiple_myeloma_differential_diagnosis#cite_ref-pmid28934935_2-0) Zuo QY, Wang H, Li W, Niu XH, Huang YH, Chen J; et al. (2017). ["Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients"](https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&tool=sumsearch.org/cite&retmode=ref&cmd=prlinks&id=28934935). *BMC Musculoskelet Disord*. **18** (1): 403. [doi](https://www.wikidoc.org/index.php/Digital_object_identifier):[10.1186/s12891-017-1756-1](https://doi.org/10.1186%2Fs12891-017-1756-1). [PMC](https://www.wikidoc.org/index.php/PubMed_Central) [5609032](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5609032). [PMID](https://www.wikidoc.org/index.php?title=PubMed_Identifier&action=edit&redlink=1) [28934935](https://www.ncbi.nlm.nih.gov/pubmed/28934935).

[Multiple myeloma - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378)

[Drug Therapy for Multiple Myeloma | American Cancer Society](https://www.cancer.org/cancer/types/multiple-myeloma/treating/chemotherapy.html)

[What Is Multiple Myeloma? | American Cancer Society](https://www.cancer.org/cancer/types/multiple-myeloma/about/what-is-multiple-myeloma.html)

## <https://www.cancer.org/cancer/types/multiple-myeloma/causes-risks-prevention/prevention.html>

### 

### 

### Myelodysplastic syndrome (MDS)

### DEFINITION AND DESCRIPTION

Myelodysplastic syndrome (also called myelodysplasia or more recently, myelodysplastic neoplasm) refers to a group of cancers that keep your blood (hematopoietic) stem cells from maturing into healthy blood cells. Without enough healthy blood cells, you may develop serious conditions like anemia, frequent infections and bleeding that won’t stop. Some people with MDS may develop acute myeloid leukemia (AML).

MDS is rare. It affects about 4 in 100,000 people in the U.S. each year. If you have MDS, your healthcare providers will focus treatment on slowing its progress, easing your symptoms and treating the conditions it causes.

#### Types of myelodysplastic syndrome

There are six MDS types. Healthcare providers categorize the condition after reviewing results of tests that show:

* The number of healthy red and white blood cells and platelets: People with lower-than-usual red blood cells have anemia, which may make them feel weak and short of breath.
* The number of immature blood cells or blasts: Blasts take up space in your bone marrow, leaving less room for healthy blood cells. If you don’t have enough healthy white blood cells, you may have frequent infections. If you don’t have enough healthy platelets, you may have bleeding that won’t stop.
* Sideroblasts: Sideroblasts are immature red blood cells that store iron instead of using it to make hemoglobin. Hemoglobin is a protein that helps your red blood cells carry oxygen throughout your body. It needs iron to do that. If pathologists spot sideroblasts, it means your hemoglobin isn’t working as it should.
* Chromosomal changes: Chromosomes are the parts of our cells that contain genes. Genes are made of DNA. Unusual chromosomes may mean something has affected your DNA, causing changes in your blood cell chromosomes.

| **MDS types** | **Characteristics** |
| --- | --- |
| MDS with multilineage dysplasia (MDS-MLD) | Some of the blood cells or platelets in your bone marrow are oddly shaped or look different from healthy cells. Your provider may refer to this as dysplasia. You have the normal number of blasts, but you have low levels of at least one blood cell type. If you have this subtype, you may eventually develop AML. |
| MDS with single lineage dysplasia (MDS-SLD) | At least one of the immature blood cell or platelet types in your bone marrow looks different from healthy cells or platelets. There are low levels of one or two of your blood cell types and you have the normal number of blasts in your bone marrow and few or no blasts in your blood. This type of MDS rarely becomes AML. |
| MDS with ring sideroblasts (MDS-RS) | In this type of MDS, about 15% of immature red blood cells are ring sideroblasts, and dysplasia affects one or two cell types in your bone marrow. Rarely, it turns into AML. |
| MDS with excess blasts (MDS-EB) | You may have anemia. Tests show low levels of two of your three blood cell types and that you have a significant number of blasts. About 40% of people diagnosed with MDS-EB eventually develop AML. |
| Myelodysplastic syndrome associated with an isolated del (5q) chromosome | Special tests to analyze cells show a certain chromosome part is missing. |
| Myelodysplastic syndrome, unclassifiable (MDS-U) | Tests show you have fewer blood cells than usual, or abnormal chromosomes but no other MDS signs. |

## Symptoms

You can have MDS without having any symptoms. Sometimes, people learn they have a type of this syndrome after having routine blood tests. Low levels of red blood cells (anemia) are the most common symptom. But anemia symptoms and other MDS symptoms can resemble other less serious conditions.

Check with your healthcare provider if you notice the following changes, particularly changes that don’t go away within a few weeks:

* You feel as if you can’t quite catch your breath (dyspnea).
* You feel weak or very tired, and resting doesn’t make you feel less tired.
* You notice your skin is paler than usual. If you have dark skin, your healthcare provider may check your inner eyelids and the inside of your mouth and nose for loss of color.
* You bruise or bleed more often than usual.
* You notice you have pinpoint-sized spots on your skin. This may be a sign you have petechiae, which are tiny spots of bleeding under your skin.
* You have frequent infections and fevers.

### 

### Causes of myelodysplastic syndrome

People seem to develop MDS in one of two ways: They participate in activities that increase their risk of developing the syndrome or they inherit certain conditions.

#### Activities linked to MDS

* Past treatment with chemotherapy or radiation therapy. Healthcare providers may call this therapy-related MDS or tMDS. Generally speaking, tMDS symptoms may appear five to seven years after therapy.
* Being exposed to certain carcinogens, including tobacco smoke, pesticides and solvents like benzene.
* Being exposed to heavy metals, like mercury or lead.

#### Genetic conditions linked to MDS

Between 4% and 15% of people with this condition have inherited conditions that increase the chance they’ll have the disease. Those conditions include:

* Fanconi anemia: This is a rare genetic condition where your bone marrow doesn’t produce enough healthy blood cells.
* Dyskeratosis congenita: This is another rare genetic condition where your bone marrow doesn’t produce enough healthy blood cells.
* Diamond-Blackfan anemia: This is a rare blood disorder that happens when your bone marrow doesn’t produce enough red blood cells.

## Diagnosis and Tests

Providers take several steps to diagnose myelodysplastic syndrome:

* Complete blood count (CBC) with differential: Your provider will draw blood samples to analyze your red and white blood cells, including counting the number of each white blood cell type.
* Peripheral blood smear: They’ll check your blood sample for changes in the number, type, shape and size of blood cells, and if you have too much iron in your red blood cells.
* Cytogenetic analysis: A medical pathologist looks for changes in your blood cell chromosomes by viewing a blood sample under a microscope.
* Bone marrow biopsy: To do this procedure, your provider inserts a hollow needle into your hipbone to remove bone marrow, blood and a small piece of bone for examination under a microscope.

#### What are the stages of myelodysplastic syndrome?

Providers evaluate or stage the condition based on the risk that the syndrome will become acute myeloid leukemia (AML). They use a risk rating system called the International Prognostic Scoring System. Here are factors that providers consider:

* Whether you show signs or symptoms of anemia, bleeding or infection.
* Your risk of developing leukemia.
* Certain changes in your chromosomes.
* Whether you developed MDS after receiving chemotherapy or radiation therapy for cancer.
* Your age and general health.

## Management and Treatment

Healthcare providers consider several factors when developing MDS treatment plans:

* The type of MDS you have.
* If you have MDS conditions such as anemia, bleeding or infections.
* Whether you developed MDS after receiving chemotherapy or radiation therapy for cancer.
* Your age.
* Your general health.

Treatment for myelodysplastic syndrome may include supportive care and treatment to get rid of unhealthy blood cells. Supportive care may include:

* Blood transfusion: If you have anemia, you may receive red blood cell transfusions. If you have bleeding issues, you may receive platelet transfusions.
* Erythropoiesis-stimulating agents (ESA): This treatment boosts your mature red blood cell levels.
* Antibiotics: MDS may affect your white blood cells and increase your risk of infections.

Treatments to get rid of unhealthy blood cells may include:

* Chemotherapy: Healthcare providers may use the same chemotherapy that’s used to treat AML.
* Immunosuppressive therapy: Providers may use this treatment for certain MDS subtypes. Immunosuppressive therapy suppresses overactive immune systems and may help reduce the need for transfusions.
* Stem cell transplant: Stem cell transplants replace your blood-forming cells with stem cells obtained from your blood or bone marrow or a donor’s blood or bone marrow. The stem cells are frozen and stored while you receive chemotherapy. Then, the stem cells are thawed and returned to you via intravenous infusion. Your re-infused cells then grow into and restore your blood cells.

These treatments have different side effects and complications. As you’re thinking about treatment options, ask your healthcare provider about each option’s side effects and complications.

People with myelodysplasia may benefit from palliative care. This care helps people manage MDS symptoms and treatment side effects. Just as important, it may help people manage the emotional impact of living with a chronic disease.

## 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.

## 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.

## 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.

## Differential Diagnosis

## The myelodysplastic syndromes (MDS) are a heterogenous group of neoplastic disorders of clonal hematopoietic stem cells characterized by dysplasia of major blood cell lines and ineffective hematopoiesis resulting in cytopenia. Clinical features include an increased percentage of blasts in the bone marrow and peripheral blood accounting for less than 20% of nucleated cells.

## MDS can be difficult to diagnose because of overlap with other syndromes and clinical similarities, particularly cytopenia. Comprehensive diagnostic testing, including blood tests, bone marrow aspiration and biopsy, and karyotyping, is required to rule out other potential causes of cytopenia.

## Common mimics of MDS that cause cytopenia or morphologic abnormalities of blood cells include the following:

* Cobalamin, copper, or folate deficiencies
* Congenital syndromes such as Fanconi anemia and X-linked sideroblastic anemia
* Excessive alcohol consumption
* HIV infection
* Immune-mediated cytopenias, such as aplastic anemia and large granular lymphocytic leukemia
* Medications such as methotrexate
* Myeloproliferative neoplasms (some of which may co-occur with MDS in overlap syndromes)

Many entities should be considered in the differential diagnosis during an evaluation for MDS.

**EPIDEMIOLOGY**

MDS) are a heterogenous group of rare hematological neoplasms affecting the production of normal blood cells in the bone marrow. Damage to the DNA of hematopoietic stem cells results in the synthesis of abnormal red cells, white cells, and/or platelets that do not mature or function properly.

## Incidence and Prevalence of MDS

## The annual incidence of MDS in the United States is estimated to be approximately 4.9 cases per 100,000 persons, according to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program database from 2007 through 2011.

## More recent estimates indicate that the incidence of MDS is increasing, possibly as a consequence of the growing number of older individuals.3 Estimates of the incidence of MDS vary widely, ranging between 10,000 and 55,000 new cases per year.3-5 The incidence of MDS in Europe is projected to be double that in the United States.

## On the basis of the estimated annual incidence and median survival rates for MDS, the projected prevalence of MDS in the United States is between 60,000 and 120,000.

## A systematic review of the global incidence and prevalence of MDS published in 2016 analyzed data from 25 studies reporting MDS incidence and 2 reporting MDS prevalence. The global incidence of MDS ranged between 0.06 and 0.26 per 100,000. The global prevalence of MDS ranged from 0.22 to 13.2 per 100,000 for all age categories, genders, and ethnicities.6 Orphanet similarly reports a global prevalence of MDS of between 1 and 9 per 100,000.

## Race/Ethnicity Factors of MDS

## Several sources indicate that MDS occurs more frequently in White individuals than in other ethnic groups.

## Epidemiologists in a study conducted at Montefiore Medical Center from 1997 to 2011 reported a greater prevalence of thrombocytopenia in Hispanic individuals with MDS in comparison with other ethnic groups; however, it was not significant.8 Median survival times were higher in Hispanic individuals and Black individuals (8.6 years and 6.2 years, respectively) than in White individuals (3.7 years).

## In a 2022 epidemiological study, researchers reported that overall survival rates were higher in individuals of African descent than in those of European or Hispanic descent.

## The epidemiology of MDS is distinct in Japan and Eastern Europe, including an increased risk in survivors of the 1945 Hiroshima and Nagasaki atomic bomb explosions that is lasting into the 21st century.

## In China and South Asia, there is a higher incidence of patients with more complex karyotypes and monosomy . In the same regions, there is less incidence of some MDS subtypes, such as refractory anemia with ring sideroblasts, than in the West. The reason is unknown but may have to do with genetics or environment.

## Age Factors of MDS

## The incidence of MDS increases with age.2-4, The onset of MDS is usually in individuals older than 65 years. The onset is most frequent in people older than 80 years.

## Disease onset before age 50 years is atypical unless it is treatment-related. The median age at the presentation of MDS is 70 years.

## However, a 2005 retrospective comparative study found that Chinese patients with MDS were diagnosed at younger ages, with a median of 49 years vs 65 to 73 years in Western countries.

## Sex Factors of MDS

## Many sources indicate that most subtypes of MDS occur more often in men than in women.2,3,11,12 The exception is the MDS subtype with isolated 5q deletion, which is more common in women.

## 

## REFERENCE

<https://www.rarediseaseadvisor.com/disease-info-pages/myelodysplastic-symdromes-epidemiology/>

<https://my.clevelandclinic.org/health/diseases/12194-cancer>

**Polycythemia vera**

**Definition and description**

Polycythemia vera (pol-e-sy-THEE-me-uh VEER-uh) is a type of blood cancer. It causes the bone marrow to make too many red blood cells. These extra cells thicken the blood, slowing its flow. This may cause serious problems, such as blood clots.

Polycythemia vera is rare. It comes on slowly. You might have it for years without knowing. Often the condition is found during a blood test done for another reason.

Without treatment, polycythemia vera can be life-threatening. But proper medical care can help ease symptoms and complications of this disease.

## signs and Symptoms

Many people with polycythemia vera don't notice symptoms. Some people get symptoms such as headache, dizziness, tiredness and blurred vision.

Clearer symptoms of polycythemia vera include:

* Itchiness, mostly after a warm bath or shower.
* Numbness, tingling, burning or weakness in the hands, feet, arms or legs.
* A feeling of fullness soon after eating.
* Bloating or pain in the left upper stomach area due to an enlarged spleen.
* Unusual bleeding, such as a nosebleed or bleeding gums.
* Painful swelling of one joint, often the big toe.
* Shortness of breath and trouble breathing when lying down.
* Bone pain.

**When to see a doctor**

Make an appointment with your healthcare professional if you have symptoms of polycythemia vera.

**Causes**

Polycythemia vera happens when a change in a gene causes a problem with making blood cells. The body typically controls the number of each of the three types of blood cells. These are red blood cells, white blood cells and platelets. But in polycythemia vera, the bone marrow makes too many of some of these blood cells.

The cause of the gene change in polycythemia vera is unknown. But it's not passed through families.

**Risk factors**

Polycythemia vera can happen at any age. But it's more common in adults over age 60. Men are more likely to get polycythemia vera than women are.

**Diagnosis and test**

Your healthcare professional takes a medical history and do a physical exam.

**Blood tests**

If you have polycythemia vera, blood tests might show:

* **More red blood cells than usual** and, sometimes, an increase in platelets or white blood cells.
* **A higher portion of red blood cells** that make up total blood volume, called hematocrit measurement.
* **Higher level of the iron-rich protein** in red blood cells that carries oxygen, called hemoglobin.

### 

### Bone marrow aspiration or biopsy

A healthcare professional who suspects that you have polycythemia vera might suggest getting a sample of your bone marrow through a bone marrow aspiration or biopsy.

A bone marrow biopsy involves taking a sample of the spongy tissue in bone marrow. A bone marrow aspiration often is done at the same time to get a sample of the liquid portion of your marrow.

### Gene testing

Study of your bone marrow or blood might show the gene change that's linked with the disease.

## 

## Treatment

There's no cure for polycythemia vera. Treatment aims to lower your risk of complications. Treatments also might ease your symptoms.

### Blood withdrawals

The most common treatment for polycythemia vera is having blood withdrawn often. This is done using a needle in a vein, called phlebotomy. It's the same procedure used for donating blood.

This lowers your blood volume and reduces the number of excess blood cells. How often you need to have blood withdrawn depends on how severe your condition is.

### Treatments to reduce itching

If the condition causes itching, medicines such as antihistamines or treatments with ultraviolet light might give you relief.

Medicines that are used to treat depression, called selective serotonin reuptake inhibitors (SSRIs), helped relieve itching in clinical trials. SSRIs include paroxetine (Brisdelle, Paxil) or fluoxetine (Prozac, Symbyax).

### 

### Medicines that lower the number of red blood cells

If phlebotomy doesn't help enough, these medicines can lower the number of red blood cells in your blood:

* Hydroxyurea (Droxia, Hydrea, Siklos).
* Interferon alfa-2b (Intron A).
* Ruxolitinib (Jakafi).
* Busulfan (Busulfex, Myleran).

### Heart medicines

Your healthcare professional also will likely prescribe medicines to control risk factors for heart and blood vessel disease. These include high blood pressure, diabetes and high cholesterol.

You also might take a low dose of aspirin to reduce your risk of blood clots. Low-dose aspirin also may help reduce burning pain in your feet or hands.

## 

## Self care

Here are ways to feel better if you have polycythemia vera:

* **Exercise.** Gentle exercise, such as walking, can improve blood flow. This helps lower the risk of blood clots. Leg and ankle stretches and exercises also can improve blood flow.
* **Don't use tobacco.** Using tobacco can narrow your blood vessels. This raises the risk of heart attack or stroke due to blood clots.
* **Don't go places with low oxygen levels.** Living at high altitudes, skiing or climbing in mountains all reduce the oxygen levels in your blood.
* **Be good to your skin.** To reduce itching, bathe in cool water, use a gentle cleanser and pat your skin dry. Adding starch, such as cornstarch, to your bath might help. Don't use hot tubs or heated whirlpools. Don't take hot showers or baths.  
  Try not to scratch. Scratching can hurt your skin and raise the risk of infection. Use lotion on your skin to keep it moist.
* **Take care in hot and cold temperatures.** Poor blood flow increases your risk of injury from hot and cold temperatures. In cold weather, always wear warm clothing. Keep your feet and hands warm.  
  In hot weather, protect yourself from the sun. Drink plenty of liquids.
* **Watch for sores.** Poor blood flow can make it hard for sores to heal. Look at your hands and feet often. Tell your healthcare professional about any sores.

**Complications**

Possible complications of polycythemia vera include:

* **Blood clots.** Increased blood thickness, decreased blood flow and atypical platelets raise the risk of blood clots. Blood clots can cause a stroke or a heart attack. Or clots can block an artery in the lungs or a vein deep within a leg muscle or in the belly.
* **Enlarged spleen.** The spleen helps the body fight infection. It also filters waste, such as old or damaged blood cells. The extra blood cells that occur with polycythemia vera make the spleen work harder. That causes it to enlarge.
* **Problems due to high levels of red blood cells.** Too many red blood cells can lead to other complications. These include open sores on the inside lining of the stomach, upper small intestine or esophagus, called peptic ulcers, and swelling of the joints, called gout.
* **Other blood disorders.** In rare cases, polycythemia vera can lead to other blood diseases. These include a disorder in which scar tissue replaces bone marrow, a condition in which stem cells don't mature or work as they should, and cancer of the blood and bone marrow, called acute leukemia.

**DIFFERENTIAL DIAGNOSIS**

Primary polycythemia vera (PV) must demonstrate increased production in all three cell lines to make the diagnosis. Increased red blood cell mass alone is not enough for diagnosis because other conditions such as chronic hypoxia and erythropoietin-secreting tumors can lead to polycythemia. Secondary polycythemia (from hypoxia or smoking) is much more common than primary PV and must be ruled out before the diagnosis of primary PV can be made. A rare mutation of the erythropoietin (EPO) receptor can mimic the basic presentation of PV, including increased red cell mass and decreased EPO. However, the mechanism is an over-sensitive receptor to EPO rather than EPO independence. Isolated granulocytosis can occur from infections or leukemoid reactions. Thrombocytosis alone can result from bleeding or iron deficiency.

Differential diagnoses to consider include:

* Essential thrombocythemia
* Chronic myelogenous leukemia
* Agnogenic myeloid metaplasia
* Chronic myelogenous leukemia
* Primary myelofibrosis
* Secondary polycythemia

**EPIDEMIOLOGY**

Polycythemia vera (PV) can affect all ethnic groups with no sex predilection, although there are slightly more cases in men than women. It can occur in all age groups, but the median age of diagnosis is 60. PV affects 0.6 to 1.6 per million people in the United States. There are fewer incidents in Japan than in the United States or Europe.

**RECOMMENDATION**

## Risk Stratification

* Patients are categorized as low-risk (age <60 years and no history of thrombosis) or high-risk (age ≥60 years and/or history of thrombosis).
* Risk classification guides treatment intensity and choice.

## Treatment for Low-Risk PV

* First-line management includes:
  + Aspirin for thrombosis prevention.
  + Phlebotomy to maintain hematocrit <45%.
* Cytoreductive therapy is not routinely recommended initially but is indicated for symptomatic patients or those with progressive disease features (e.g., pruritus, splenomegaly, thrombocytosis).
* Ropeginterferon alfa-2b (Besremi) is now a preferred first-line cytoreductive therapy option for symptomatic low-risk patients, alongside hydroxyurea and peginterferon alfa.
* Cardiovascular risk factors should be actively managed.

## Treatment for High-Risk PV

* Combination of:
  + Aspirin and phlebotomy (hematocrit <45%).
  + Cytoreductive therapy is recommended upfront.
* Preferred cytoreductive agents include:
  + Hydroxyurea
  + Ropeginterferon alfa-2b (Besremi) (recently added as preferred agent)
  + Peginterferon alfa as an alternative.
* Other agents may be considered based on patient tolerance and comorbidities.

## Ropeginterferon Alfa-2b Updates

* Ropeginterferon alfa-2b received FDA approval in 2021 and was incorporated into NCCN guidelines as a preferred first-line therapy in 2023–2025 updates.
* It is recommended for both low- and high-risk PV patients, regardless of prior treatment history.
* Clinical trials (PROUD-PV and CONTINUATION-PV) demonstrated superior hematologic response and tolerability compared to standard therapies.
* The guidelines also support its use as a substitute if peginterferon alfa-2a is unavailable.

## General Principles

* Prevention of thrombosis and bleeding through hematocrit control and aspirin is fundamental.
* Cytoreductive therapy aims to reduce elevated blood counts and disease symptoms (e.g., pruritus, splenomegaly).
* Treatment choice considers patient age, symptoms, risk factors, and tolerance.
* Management of cardiovascular risk factors is emphasized.

REFERENCE

[Polycythemia vera - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/polycythemia-vera/diagnosis-treatment/drc-20355855)

<https://www.ncbi.nlm.nih.gov/books/NBK557660/#article-27403.s10>

### Myeloproliferative neoplasms (MPN)

**Definition and description**

Myeloproliferative neoplasms (MPNs) are rare, potentially life-threatening blood cancers that happen when your bone marrow makes too many blood cells. Blood cells include red blood cells, white blood cells and platelets. They’re made in the spongy tissue inside of your bones. With a myeloproliferative neoplasm, something goes wrong in the blood cell production process.

Myeloproliferative (pronounced “MY-eh-loh-proh-LIH-feh-ruh-tiv) neoplasms develop very slowly, so people may have them for years before noticing symptoms. Myeloproliferative neoplasms are also called chronic myeloproliferative neoplasms or myeloproliferative disorders. Chronic means that a condition is long-term. Rarely, a myeloproliferative neoplasm may turn into a more serious disease.

There are treatments that ease symptoms and reduce the risk of a myeloproliferative neoplasm developing into a more serious disease.

### Types of myeloproliferative neoplasms

Depending on the type of myeloproliferative neoplasm, your bone marrow may make too many red blood cells, white blood cells, platelets or a combination of cell types. The cells often behave differently from healthy blood cells.

### Who do myeloproliferative neoplasms affect?

Your age and sex are the most significant predictors of how likely you are to have a myeloproliferative neoplasm.

* Age: Myeloproliferative neoplasms affect multiple age groups, but they’re most common in people in their 50s, 60s or older.
* Sex: Polycythemia vera is generally more common in males. Essential thrombocythemia is more common in females. The remainder of the myeloproliferative neoplasms occur equally in both sexes.

### How do myeloproliferative neoplasms affect my body?

These blood diseases happen when your bone marrow makes more of a certain blood cell type than your body can use. The impact on your body varies based on the blood cell type affected. For example, one type of myeloproliferative neoplasm increases your risk of heart attack or stroke. Another type may cause anemia.

To understand these rare diseases, it may help to have some information about your bone marrow and blood cell production. All blood cells start as stem cells in your bone marrow. Your bone marrow is soft, sponge-like tissue in the center of your bones. It makes cells that may become myeloid stem cells or lymphoid stem cells.

Lymphoid stem cells become white blood cells that help fight infection. Myeloid stem cells can become red blood cells that carry oxygen throughout your body, white blood cells or platelets, which prevent excessive bleeding.

Like all cells, stem cells take instruction from genes that help dictate cells’ form and function. Normally, your bone marrow makes stem cells that divide and multiply as needed. These stem cells follow directions from genes that help regulate cell development.

When these genes mutate, they send new instructions to certain stem cells, telling the cells to keep on dividing and multiplying. Eventually, these stem cells become mature blood cells that pile up in your bone marrow or bloodstream, affecting blood flow. Blocked blood flow can cause serious medical conditions.

### What are common myeloproliferative neoplasms?

The three most common types are polycythemia vera, essential thrombocythemia and primary myelofibrosis.

#### Polycythemia vera

This is the most common myeloproliferative neoplasm. It makes your bone marrow produce too many red blood cells. The excess red blood cells make your blood thick, so blood moves more slowly through your bloodstream. People with polycythemia vera are likely to develop blood clots that may cause heart attack and stroke. Very rarely, polycythemia vera may progress or become serious blood diseases, including acute leukemia.

#### Myelofibrosis

This is the most aggressive myeloproliferative neoplasm. In myelofibrosis, your bone marrow produces abnormal stem cells that become inflamed and make scar tissue. Over time, your bone marrow fills up with scar tissue. The scar tissue keeps your bone marrow from making enough red blood cells to carry oxygen throughout your body, and you may develop anemia. Your bone marrow also falls behind on platelet production. Platelets help to slow and stop excessive bleeding. Some people with myelofibrosis will develop acute myeloid leukemia.

#### Essential thrombocythemia

Essential thrombocythemia happens when your bone marrow makes too many platelets. If a blood vessel ruptures, platelets make blood clots that slow or stop bleeding. In essential thrombocythemia, your bone marrow makes platelets even when there’s no need for them. These excess platelets become blood clots that increase your risk of having a heart attack or a stroke. Like other myeloproliferative neoplasms, essential thrombocythemia symptoms develop very slowly. Most people learn they have this disease when routine blood tests show high platelet levels. Some people with essential thrombocythemia may develop leukemia.

### What are other types of myeloproliferative neoplasms?

Other MPN types include:

* Chronic eosinophilic leukemia (CEL) involves the overproduction of white blood cells called eosinophils. Usually, it progresses slowly. In rare cases, CEL can become a serious form of cancer called acute myeloid leukemia (AML). CEL is also called hypereosinophilic syndrome.
* Chronic myelogenous leukemia (CML) involves an overproduction of white blood cells called granulocytes. These cells accumulate, making it harder for your bone marrow to make other blood cells your body needs.
* Chronic neutrophilic leukemia (CNL) involves an overproduction of white blood cells called neutrophils.
* Myeloproliferative neoplasm, unclassifiable (MPN-U), is a type of myeloproliferative neoplasm that doesn’t fit into the other categories. It may involve an overproduction of various blood cell types, including white blood cells, red blood cells or platelets.

## Symptoms and Causes

You likely won’t notice symptoms in the early stages. As your condition progresses, you may notice signs of an enlarged spleen (splenomegaly). Splenomegaly feels like fullness, pressure or discomfort below your ribs on your left side, where your spleen is located. While splenomegaly is a common symptom of most myeloproliferative neoplasms, it’s a less common symptom of essential thrombocytopenia.

Other symptoms depend on the specific myeloproliferative neoplasm.

#### Chronic eosinophilic leukemia

The most common symptom is a rash. You may also feel tired and feverish. Other symptoms depend on what body parts are affected by your high eosinophil levels.

#### Chronic myelogenous leukemia and chronic neutrophilic leukemia

Symptoms may include:

* Bone pain.
* Night sweats.
* Fever and fatigue.
* Bruising easily.
* Loss of appetite and weight loss.

#### Essential thrombocythemia

Symptoms may include:

* Bruising easily.
* Unexplained bruising or bleeding from your nose, mouth and gums.
* Bleeding from your stomach or intestines.
* Blood in your pee.

#### Polycythemia vera

Symptoms may include:

* Headaches.
* Dizziness.
* Fatigue.
* Blurred or double vision.

#### 

#### 

#### Primary myelofibrosis

You may experience symptoms of anemia (fatigue, weakness, shortness of breath). Other signs and symptoms may include:

* Pale skin.
* Night sweats.
* Fevers.
* Itchy skin.
* Abdominal fullness or filling up right away when you eat (early satiety).
* Weight loss.
* Bone pain.

### Causes of myeloproliferative neoplasms

All myeloproliferative neoplasms are acquired genetic disorders. This means you can’t inherit these diseases from your biological parents. These diseases happen when genes that regulate cell growth mutate or change and your blood cell development goes wrong.

Medical researchers have made the following discoveries about the genetic mutations that cause myeloproliferative neoplasms:

* Mutations associated with Janus kinases (JAK): Polycythemia vera, primary myelofibrosis and essential thrombocythemia often involve genetic mutations associated with a protein called Janus kinase 2 (JAK2). The mutation may cause cells to multiply out of control.
* Mutations associated with the *MPL* gene or *CALR* gene: People with essential thrombocythemia and primary myelofibrosis often have mutations in their *MPL* gene or *CALR* gene.
* Chromosome errors: People with chronic myelogenous leukemia (CML) have a specific error involving their chromosomes. A chromosome is a structure that contains genes. With CML, a piece of one chromosome swaps places with another chromosome, forming the “Philadelphia chromosome.”

These discoveries don’t clarify what causes genetic changes to take place. Still, they help healthcare providers make a diagnosis and develop treatments targeting genetic mutations.

### Risk factors associated with myeloproliferative neoplasms

Family history, age and sex may increase the risk of developing MPN.

Researchers have also found links between myeloproliferative neoplasms and certain toxins and radiation exposure. Some studies show people exposed to high levels of radiation and certain toxins like benzene have an increased risk of developing myeloproliferative neoplasms, like polycythemia vera, primary myelofibrosis and chronic myelogenous leukemia.

## Diagnosis and Tests

A healthcare provider will collect a detailed medical history and perform a physical exam to check for signs and symptoms of a myeloproliferative neoplasm. They’ll run tests on your blood and bone marrow to make a diagnosis.

* Complete blood count (CBC): This test measures all blood cell levels. In essential thrombocythemia, providers evaluate platelet levels. In polycythemia vera, they look for increased hemoglobin — the protein in red blood cells — as well as white blood cells and platelets.
* Peripheral blood smear (PBS): This test can show abnormal cell shapes that may indicate a condition. Blood chemistry tests can detail how much of a specific type of chemical is in your blood (proteins, enzymes, glucose, etc.). These numbers provide clues about how your organs are functioning, which may suggest a myeloproliferative neoplasm.
* Bone marrow biopsy: Your provider may do bone marrow aspiration or bone marrow biopsy. In this test, they remove a sample of bone marrow to check your blood cells. Then, medical pathologists examine blood cells and tissue under a microscope, looking for differences between normal and abnormal cells. They’ll see if you have an unusual number of stem cells. They’ll also look for changes in chromosomes and other signs of genetic mutations that may indicate you have a specific type of myeloproliferative neoplasm.
* Genetic testing:Providers may analyze your blood cells, looking for changes in the genes that may affect blood cell production.

## Management and Treatment

Allogeneic stem cell transplantation is the only known cure for these diseases. Unfortunately, many people can’t have stem cell transplantations because they may not be able to go through the strenuous stem cell transplant process.

Your healthcare provider will provide treatments that manage your condition by reducing the number of blood cells, providing symptom relief and preventing complications. There are some treatments that can lead to remissions. MPN treatments vary by type:

* Chronic eosinophilic leukemia: Your provider will work to reduce your eosinophil levels with chemotherapy, corticosteroids or immunotherapy.
* Chronic myelogenous leukemia: The most common treatment is targeted therapy that prevents cells from multiplying out of control. Other treatments include chemotherapy, immunotherapy, radiation therapy and stem cell transplants.
* Chronic neutrophilic leukemia: Treatments may include chemotherapy, immunotherapy and stem cell transplants.
* Essential thrombocythemia: If you don’t have symptoms, your provider may choose to monitor your condition closely instead of prescribing treatments. If you have symptoms, you may need to take a treatment that prevents cells from multiplying out of control. You may need to take medicine to reduce your risk of blood clots or to prevent your bone marrow from making too many platelets.
* Polycythemia vera: Phlebotomy is the most common procedure to treat polycythemia vera. Your healthcare provider will regularly remove blood (like a blood draw) to reduce your blood volume and remove excess red blood cells. If you have symptoms, you may have targeted therapy that prevents cells from multiplying out of control. You may also take medicine to reduce your risk of blood clots (like aspirin) or to reduce your number of red blood cells.
* Primary myelofibrosis: Your provider may decide to monitor your condition closely if you aren’t experiencing symptoms. Treatments may include procedures or drugs to treat anemia. For example, you may need a blood transfusion if your bone marrow isn’t making enough red blood cells. You may take medicines that stimulate your bone marrow to produce more blood cells. Other treatments may include targeted therapy, chemotherapy, immunotherapy, radiation therapy and stem cell transplant.

## Outlook / Prognosis

Experiences vary based on many factors, including the type of myeloproliferative neoplasm, how early your condition was diagnosed and how you respond to treatment. With careful monitoring and treatment, many people live for several years. There’s no single prognosis or expected outcome for these conditions. In general, people diagnosed with MPN are alive five years later. Survival rates for specific MPNs are:

* Chronic myelogenous leukemia: The effectiveness of new targeted therapies has significantly increased the survival rate associated with CML. The five-year survival rate for CML is 90%.
* Chronic neutrophilic leukemia and polycythemia vera: With careful management, many people live 20 years, on average, following their diagnosis.
* Essential thrombocythemia: Many people live many years with essential thrombocythemia when they take medications that prevent life-threatening complications, like blood clots.
* Primary myelofibrosis: Most people with primary myelofibrosis are still alive five to 10 years after a diagnosis.

If you have this condition, ask your healthcare provider to explain your prognosis. They know all the factors that affect prognosis. Just as important, they know you, including risk factors like your age and overall health that affect your prognosis.

#### Are these diseases fatal?

On their own, these aren’t fatal diseases, but some may cause life-threatening conditions such as heart attack or stroke.

## Living With

Myeloproliferative neoplasms are a complex group of diseases with multiple treatment options that sometimes cause side effects. Similarly, various complications can arise depending on your condition. It’s important to know what signs or symptoms you should be aware of. Talk to your provider so you understand your diagnosis and can make care decisions.

### How do I take care of myself?

It can be confusing living with a myeloproliferative neoplasm. You may feel fine and wonder if there’s anything you can do to prevent symptoms. If you’re receiving treatment, you may need help managing treatment side effects and symptoms. Either way, you’ll likely be living with your disease for years to come. Here are some suggestions that may help:

* Understand your health situation:Many myeloproliferative neoplasm symptoms resemble less serious conditions. Some symptoms may be signs of serious medical complications. It may be hard to tell the difference and you may worry you’re missing important clues about your health. Ask your healthcare provider to explain how the disease may affect you. Knowing what to expect may help you feel more confident about your situation.
* Manage your stress:It can be stressful living with a long-term illness. If you’re feeling anxious about your situation, talk to your provider about your concerns. They’ll explain what they’re doing to help you now and what they’ll do to help you in the future.
* Eat balanced healthy meals:Eating well will give you the energy to manage your condition. If you need help developing healthy eating habits, ask to speak with a nutritionist.
* Get some exercise:Exercise is a great way to manage stress.
* Find some support: Myeloproliferative neoplasms are rare diseases. Support groups may be a way to connect with and talk to people who know what you’re going through.

### When should I see my healthcare provider?

If you have a myeloproliferative neoplasm but don’t have symptoms, contact your healthcare provider if you notice changes in your body that may indicate you’re developing symptoms.

**DIFFERENTIAL DIAGNOSIS**

* Chronic myelogenous leukemia
* Chronic lymphocytic leukemia
* Chronic myelomonocytic leukemia
* Juvenile myelomonocytic leukemia
* Acute myeloid leukemia
* Acute lymphoblastic leukemia
* Leukemoid reactions/hyperleukocytosis
* Essential thrombocytosis
* Secondary thrombocytosis
* Juvenile myelomonocytic leukemia
* Mastocytosis
* Hypereosinophilic syndrome
* Primary myelofibrosis
* Non-Hodgkin lymphoma
* Myelodysplastic syndromes
* Multiple myelomas
* Splenomegaly

**COMPLICATION**

Thrombosis and hemorrhagic events are the most common complications in MPNs. Other complications based on diseases are as follows:

*Chronic myeloid leukemia (CML)*: CML patients if not treated are at increased risk of blast transformation.

*Polycythemia vera (PV)*: Arterial and venous thrombosis and thromboembolic complications may manifest as transient ischemic stroke (TIA)/stroke and pulmonary embolism, myocardial infarction, and hemorrhage. Some patients with PV may present as acquired von Willebrand disease, and they have an increased tendency for bleeding, particularly if they are taking aspirin. Post-PV myelofibrosis and transformation to AML or MDS are other complications of PV. Erythromelalgia is the microvascular complication of PV which manifests as pallor, erythema, or cyanosis of the hands and feet.

*Essential thrombocythemia (ET)*: Small and large vessel thrombosis, hemorrhage, thromboembolic complications such as stroke, pulmonary embolism, myocardial infarction, pulmonary hypertension, and priapism.

*Primary myelofibrosis (PMF)*: Portal hypertension, GI bleeding, spinal cord compression, bleeding, respiratory distress, transformation to acute leukemia, thrombotic events, infections, and pulmonary hypertension.

**EPIDEMIOLOGY**

*Chronic myeloid leukemia*: It comprises 0.5% of all new cancer cases in the United States. As per recent SEER (Surveillance, Epidemiology, and End Results) national cancer database from the US, CML is commonly diagnosed in older age groups, ranging from 65 to 74 years, and the median age of diagnosis is 65 years. It is more common in males, with an incidence rate of about 2.4 new cases per 100,000 versus 1.4 new cases per 100,000 in females. About 67.6% of patients have a 5-year survival rate, and the median age of death is about 77 years.

*Polycythemia vera*: The median age of diagnosis of PV is 60 years. It is more prevalent in males as compared to females, with a male to female ratio of 1.8: 1. The estimated incidence of PV ranges from 0.4 to 2.8 per 100,000 per year.

*Essential thrombocythemia*: The median age for diagnosis of ET is 60 years. It is more common in females, with a male to female ratio of 1:2. The estimated incidence of ET ranges from 1 to 2.5/100,000/year, and incidence increases with increasing age.

*Primary myelofibrosis*: The median age at the diagnosis is 67 years. The incidence rate varies from 0.8 to 2.1/100,000/year.

Other MPNs such as CNL, CEL, and unclassified MPN are rare; exact incidence and prevalence are not known due to the rarity of the disorders.

REFERENCES

<https://www.ncbi.nlm.nih.gov/books/NBK531464/#article-25454.s10>

[Myeloproliferative Neoplasm: Symptoms, Types & Treatment](https://my.clevelandclinic.org/health/diseases/24144-myeloproliferative-neoplasms)

### 

### NON-MALIGNANT BLOOD DISORDERS

### Blood disorders

Blood disorders are conditions that keep parts of your blood from doing their jobs:

* Your red blood cells carry oxygen throughout your body.
* Your white blood cells help protect your body from infection.
* Your platelets help your blood to clot so you don’t bleed more than normal.

Blood disorders may be cancerous or noncancerous. This article focuses on noncancerous blood disorders.

You may inherit a noncancerous blood disorder or develop one because you have an underlying condition that affects your blood.

Some blood disorders may not cause symptoms or require treatment. Others are chronic (lifelong) illnesses that require treatment but typically won’t affect how long you’ll live. Other blood disorders are serious illnesses that can be life-threatening.

Healthcare providers treat blood disorders by managing symptoms and treating any underlying conditions.

#### How do blood disorders affect my body?

In general, noncancerous blood disorders are conditions that affect your blood cells and platelets and cause issues that may:

* Increase your risk of blood clots. Factor V Leiden, an inherited blood disorder, is an example of a blood clotting disorder.
* Make you bleed more than normal because your blood doesn’t form blood clots. Inherited hemophilia is an example of a bleeding disorder.

#### What are common blood clotting disorders?

A blood clotting disorder affects your platelets or your clotting factors (coagulation factors). Clotting factors are proteins in your blood. Your platelets and clotting factors make blood clots, which control bleeding. Blood clotting disorders may be called a hypercoagulable state or thrombophilia. Blood clotting disorders include:

* Prothrombin gene mutation: This inherited disorder increases your risk of developing abnormal blood clots in your veins (deep vein thrombosis) and lungs (pulmonary embolism).
* Antiphospholipid syndrome: This rare autoimmune disorder, which often affects people who have lupus, can cause blood clots in several areas of your body.
* Protein S deficiency: Protein S is a natural anticoagulant in your blood. Anticoagulants prevent blood from clotting. Protein S helps keep other proteins from making too many blood clots. This is a rare inherited disorder.
* Protein C deficiency: Like protein S, protein C is a natural anticoagulant that protects you from developing too many blood clots.
* Antithrombin deficiency: This inherited disorder increases your risk of deep vein thrombosis.
* Paroxysmal nocturnal hemoglobinuria: This rare blood disorder happens when your immune system attacks your red blood cells, increasing your risk of blood clots.
* Disseminated intravascular coagulation (DIC): DIC is a rare blood clotting disorder that may cause uncontrollable bleeding or clotting.

Some people with blood clotting orders have an increased risk of stroke and heart attack. Call your local emergency line if you think you’re having a pulmonary embolism because you have chest pain and difficulty breathing. Heart attack and stroke are other medical conditions that need emergency treatment.

#### What are common bleeding disorders?

Bleeding disorders happen when your blood doesn’t clot normally, causing you to bleed more than usual. Bleeding disorders include:

* Von Willebrand disease: This condition is the most common bleeding disorder in the U.S. Most people who have von Willebrand disease inherited a mutated gene from one of their biological parents. Some people develop this condition as a complication of certain cancers, autoimmune disorders, and heart and blood vessel diseases.
* Inherited hemophilia: This rare genetic condition may make you bleed more than usual. There are three types of hemophilia: Type A or classic hemophilia, Type B or Christmas disease and Type C (Rosenthal syndrome).
* Thrombocytopenia: This condition happens when you have a low platelet count. Immune thrombocytopenia (ITP) and thrombotic thrombocytopenic purpura (TTP) are examples of diseases that cause thrombocytopenia.
* Fibrinogen deficiency conditions: Fibrinogen is another protein that helps your blood clot.If you don’t have enough fibrinogen or your fibrinogen doesn’t work as it should, you may have abnormal bleeding or clotting issues.

### What is the most common type of blood disorder?

Anemia represents the most common type of noncancerous blood disorder. The U.S. Centers for Disease Control and Prevention estimates about 3 million people in the U.S. have some type of anemia. Anemia happens when you don’t have enough healthy red blood cells. Some types of anemia are inherited, but people may also acquire or develop them.

#### Acquired anemias

* Pernicious anemia: Pernicious anemia, one of the causes of vitamin B12 deficiency, is an autoimmune condition that prevents your body from absorbing vitamin B12.
* Iron-deficiency anemia: As its name implies, iron-deficiency anemia happens when your body doesn’t have enough iron to make hemoglobin. Red blood cells need hemoglobin to carry oxygen throughout your body.
* Megaloblastic anemia: Megaloblastic anemia is a type of anemia that can happen when you don’t get enough vitamin B12 and/or vitamin B9 (folate).
* Aplastic anemia: This anemia happens when stem cells in your bone marrow don’t make enough blood cells.
* Autoimmune hemolytic anemia: In autoimmune hemolytic anemia, your immune system attacks your red blood cells.
* Macrocytic anemia: This anemia happens when your bone marrow makes unusually large red blood cells. Macrocytic anemia may be caused by myelodysplastic syndrome, low folate, low B12 vitamin, liver disease, alcohol use and certain medications.
* Normocytic anemia: In this type of anemia, you have fewer red blood cells than usual. There are many causes of normocytic anemia.

#### Inherited anemias

* Sickle cell anemia: Sickle cell anemia changes your red blood cells’ shape, turning round flexible discs into stiff and sticky sickle cells that block blood flow.
* Fanconi anemia: Fanconi anemia is a rare blood disorder. Anemia is one sign of Fanconi anemia.
* Diamond-Blackfan anemia: This inherited disorder keeps your bone marrow from making enough red blood cells.
* Thalassemia: In thalassemia, your body produces less hemoglobin, resulting in small red blood cells and anemia.

##### Other anemia types

Some types of anemia may be inherited but can also be acquired:

* Hemolytic anemia: In this anemia, your red blood cells break down or die faster than usual.
* Sideroblastic anemia: Sideroblastic anemia results from abnormal iron use during red blood cell development.
* Microcytic anemia: This anemia happens when your red blood cells don’t have enough hemoglobin so they’re smaller than usual. Microcytic anemia occurs with iron deficiency, thalassemia, sideroblastic anemia and in some cases of anemia of chronic disease.

## Symptoms of blood disorder

Blood disorder symptoms depend on the specific blood disorder and its impact on your blood.

For example, most people with anemia have the following symptoms:

* Fatigue and weakness.
* Dizziness.
* Skin that’s paler than usual.
* Fast heartbeat (heart palpitations).
* Shortness of breath.

#### Common bleeding disorder symptoms

The most common symptom is excessive and continuous bleeding. You may want to talk to your healthcare provider if you have any of the following symptoms:

* Nosebleeds: These are nosebleeds that last longer than 10 minutes and happen five or more times a year.
* Excessive bleeding: Cuts or injuries that bleed longer than 10 minutes.
* Internal bleeding: This may cause joint pain.
* Bruises: Bruising that happens for no apparent reason or after a minor injury.
* Post-surgery bleeding: Heavy bleeding after any kind of 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.

#### Common blood clotting disorder symptoms

Blood clotting disorders increase your risk of developing blood clots in your veins, lungs and other areas of your body. People with blood clotting disorders may have the following symptoms:

* Swelling, tenderness and pain in your leg can mean you have deep vein thrombosis.
* Chest pain with shortness of breath can mean a possible pulmonary embolism.
* Heart attack.
* Stroke.

### 

### most common cause of blood disorders

the causes and risk factors associated with non cancerous blood disorders, also known as **benign hematologic conditions** or **hematologic disorders**. Understanding the underlying factors that contribute to the development of these conditions is essential for prevention and early detection.

* *Genetic Factors:* Certain non cancerous blood disorders have a genetic component, meaning they can be inherited from parents or other family members. Mutations in specific genes can increase the risk of developing these conditions.
* *Environmental Influences:* Environmental factors such as exposure to toxins, radiation, or certain medications can play a role in the development of non cancerous blood disorders. Prolonged exposure to these factors can disrupt the normal functioning of blood cells.
* *Hemoglobinopathies:* Hemoglobinopathies are a group of inherited blood disorders that affect the production or structure of hemoglobin, the protein responsible for carrying oxygen in the blood. Conditions such as sickle cell anemia and thalassemia fall under this category.
* *Autoimmune Disorders:* Some non cancerous blood disorders are caused by an overactive immune system that mistakenly attacks healthy blood cells. Conditions like immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) fall into this category.
* *Other Risk Factors:* Certain lifestyle factors, such as smoking, excessive alcohol consumption, and a sedentary lifestyle, can increase the risk of developing non cancerous blood disorders. Additionally, certain infections and chronic illnesses may also contribute to the development of these conditions.

There’s no single cause for blood disorders. Some people inherit blood disorders. Other blood disorders happen because people develop a condition that affects their blood.

## Diagnosis and Tests

Healthcare providers will do physical examinations, ask you about your medical history and your symptoms. They may do several blood tests.

#### Red blood cell tests

Red blood cells carry oxygen from your lungs to your body’s tissues. Your tissues produce energy with the oxygen and release carbon dioxide. Your red blood cells take the carbon dioxide waste to your lungs for you to exhale.

Providers will take blood samples to evaluate your red blood cell count and your red blood cell components or parts. They may do tests to see what your red blood cells look like under a microscope. Red blood cell tests may include:

* Hemoglobin test: Hemoglobin is the main component of red blood cells. The test is often used to detect anemia.
* Hematocrit test: This test measures the percentage of red blood cells in your blood.
* Reticulocyte count: Reticulocytes are immature red blood cells. This test checks to see if your bone marrow is producing enough healthy red blood cells.

#### White blood cell tests

White blood cells represent about 1% of your blood. They protect your body against infection. Abnormal white blood cell levels may be signs of several medical conditions.

For example, a high white blood cell count (leukocytosis) may mean you have an infection, inflammation or cancer. A low white blood cell count (leukopenia) may be a sign of conditions ranging from vitamin deficiencies to cancer.

There are three kinds of white blood cells — granulocytes, monocytes and lymphocytes. Granulocytes include three sub-types of white blood cells — eosinophils, basophils and neutrophils. Your healthcare provider may do a complete blood count (CBC) with differential to evaluate each white blood cell type:

* Eosinophils: Eosinophils protect your body from infections. Blood tests may show high eosinophil levels (eosinophilia). Eosinophilia may be a sign of underlying medical conditions.
* Basophils: Basophils protect your body against allergens and other intruders. Basophilia happens when your body produces too many basophils. A high basophil count may be a sign of certain blood cancers.
* Neutrophils: Neutrophils are the most common white blood cell type. Neutrophils are the first responders to fight infection. Low neutrophil counts are neutropenia. Neutropenia may increase your risk of serious infection.
* Monocytes:These white blood cells find and destroy germs. High levels of monocytes (monocytosis) may be a sign of infectious diseases.
* Lymphocytes: There are two main types of lymphocytes: T lymphocytes (T cells) manage your body’s immune system response. They attack and destroy infected cells and other intruders; B lymphocytes (B cells) make antibodies. Antibodies are proteins that target viruses, bacteria and other foreign invaders.

#### Platelet tests

Platelets, also called thrombocytes, help make blood clots and control bleeding. Tests to evaluate your platelet health may include:

* Platelet count: This test measures the number of platelets in your blood.
* Mean platelet volume (MPV) test: This blood test measures the average size of your platelets.
* Peripheral blood smear (PBS): Your provider may use this test to examine your platelets under a microscope. (They also use this test to examine your white and red blood cells.)

## Management and Treatment

In general, healthcare providers focus on identifying and treating underlying conditions that cause blood disorders. They also treat blood disorder symptoms. Treatments may include:

* Watchful waiting: Some blood disorders don’t cause noticeable symptoms. If that’s your situation, your provider will monitor your overall health, paying close attention to any new signs or symptoms that you’re developing a blood disorder.
* Blood and platelet transfusions:Providers may use blood transfusions to boost red blood cell levels for people with severe forms of anemia. They may use platelet transfusions to help with blood clotting issues.
* Anticoagulants: These medications help with blood clotting disorders by keeping your blood from clotting too easily.
* Growth factor supplementation: This treatment stimulates your bone marrow so it makes additional red and white blood cells. Erythropoietin-stimulating agents (ESA) are examples of growth factor supplements.
* Corticosteroids:This treatment suppresses your immune system. Providers may use steroids to treat autoimmune hemolytic anemia.

These treatments have different side effects. Ask your provider about treatment side effects. They’ll help you manage them.

## Prevention

That depends on the specific disorder. Some blood disorders are inherited, which means you can’t prevent them. Others are caused by underlying conditions that you may or may not be able to prevent. While you can’t always prevent blood disorders, there are steps you can take to reduce your risk of developing complications.

#### How can I reduce my risk of developing these disorders?

Taking care of your overall health may reduce your risk of developing conditions that cause blood disorders. Suggestions include:

* Eat a healthy diet rich in vitamins and minerals:This includes foods with iron such as eggs, turkey, lean beef and organ meats like kidney and liver. Legumes, including black beans, leafy green vegetables and brown rice, are other foods that help increase your iron intake.
* Stay active:Regular exercise helps support your immune system.
* Maintain a healthy weight:Talk to a healthcare provider about attaining and maintaining a weight that’s right for you.
* Take steps to prevent infection:Be sure to wash your hands well and often. Talk with your provider about the seasonal flu shot (vaccine) and any other vaccines you should consider.
* Get regular checkups: If you have a blood disorder or you may be at risk of developing a blood disorder, your provider will schedule regular appointments to check your overall health. They may do blood tests.

**COMPLICATIONS**

Non cancerous blood disorders can sometimes lead to complications that require additional medical intervention. These complications may include:

* Iron deficiency anemia
* Blood clots
* Increased risk of infections
* Organ damage or dysfunction

Regular monitoring and early detection of these potential complications are crucial to ensure timely intervention and prevent further health issues. Healthcare professionals can help individuals with non cancerous blood disorders understand the signs of complications and provide appropriate guidance on managing and preventing them.

In conclusion, non cancerous blood disorders can have a significant impact on both the physical and emotional wellbeing of individuals. By understanding the potential complications and seeking appropriate medical care, individuals with non cancerous blood disorders can effectively manage their condition and improve their overall quality of life.

## Outlook / Prognosis

Non Cancerous blood disorders vary widely. For example, many people with blood clotting disorders may have normal lifespans, but may require medication and treatment for the rest of their lives. But some blood disorders, like sickle cell anemia, may be life-threatening. People’s prognoses also depend on factors such as their age and overall health. If you have a blood disorder, ask your healthcare provider what you can expect.

### Other Therapeutic Interventions

In addition to lifestyle modifications and medication regimens, individuals with non cancerous blood disorders may benefit from other therapeutic interventions. These interventions aim to alleviate symptoms, improve overall health, and optimize well-being. Some examples of complementary therapies and interventions include:

* *Physical Therapy:* Physical therapy exercises can help manage pain, improve mobility, and enhance muscle strength.
* *Nutritional Counseling:* Working with a registered dietitian can ensure the individual is consuming a well balanced diet that meets their specific nutritional needs.
* *Counseling or Support Groups:* Seeking emotional support through counseling or joining support groups can help individuals cope with the challenges associated with their condition.

By incorporating these therapeutic interventions alongside lifestyle modifications and medication regimens, individuals with non cancerous blood disorders can achieve a comprehensive approach to managing their condition.

| **Treatment Option** | **Description** |
| --- | --- |
| Lifestyle  Modifications | Including a balanced diet, regular exercise, stress management, avoiding harmful substances, and maintaining a healthy weight. |
| Medication Regimens | Prescribed medications such as anticoagulants, immunosuppressants, hormone therapy, or erythropoiesis-stimulating agents. |
| Other Therapeutic Interventions | Physical therapy exercises, nutritional counseling, counseling or support groups. |

### Strategies for Self-Care

Self-care plays a crucial role in managing non cancerous blood disorders. Here are some strategies to consider:

* *Prioritize a healthy lifestyle:* Maintain a well-balanced diet, exercise regularly, and get enough sleep to boost overall health.
* *Monitor your condition:* Keep track of symptoms and any changes in your health. Regularly check your blood counts if necessary.
* *Stay consistent with medication:* Take prescribed medications as directed by your healthcare provider and ensure timely refills.
* *Manage stress:* Find healthy ways to cope with stress, such as through relaxation techniques, hobbies, or counseling.

### How do you live with a blood disorder?

Blood disorders may change your way of life. But there are things you can do to maintain your quality of life. For example:

* Educate your family and friends: Explain how your blood disorder may affect you. That way, they’ll understand why you may not be able to do certain activities and they’ll know what to do if you have a medical emergency.
* Consider wearing a medical alert bracelet: In the event of severe illness or injury, wearing this bracelet tells healthcare providers about your condition so they can give you the care you need.
* Eat an iron-rich diet: Eating a healthy diet can help anyone living with a blood disorder.
* Treat any bleeding right away: If you have a bleeding disorder, your healthcare provider may prescribe medication (factor) to help your blood clot. People with bleeding disorders should treat bleeding quickly by taking medication as prescribed.
* Reduce your risk of injury: If you have a bleeding disorder, avoid contact sports that may increase your risk of falling or being hit. Always wear your seatbelt. If you ride a bike, wear a helmet.

### When should I see a doctor?

Contact your healthcare provider if you notice changes in your body that may be signs your condition is getting worse.

#### When should I go to the emergency room?

Some noncancerous blood disorders may cause medical emergencies. People with blood clotting disorders have an increased risk of blood clots that may cause pulmonary embolism, heart attack and stroke. If you have a blood clotting disorder and have chest pain,

If you have a bleeding disorder and you’re injured, you may have trouble controlling your bleeding. If your prescribed medication doesn’t slow your blood flow, go to the emergency room.

## Epidemiology

## About 5–7% of the global population carries an abnormal haemoglobin gene. The most predominant form of haemoglobinopathy worldwide is sickle cell disease. The greatest burden of the disease lies in sub-Saharan Africa and Asia.

## The prevalence of sickle cell trait ranges between 10 and 45% in various parts of sub-Saharan Africa . In Nigeria, carrier prevalence is about 20 to 30% . SCD affects about 2 to 3% of the Nigerian population of more than 160 million. Recent estimate from a large retrospective study by Nwogoh et al. in Benin City, South-South Nigeria revealed an SCD prevalence of 2.39% and a carrier rate of about 23%

## Africa and Asia are considered as the birthplace of the sickle cell mutation. Sickle cell disease is believed to be a consequence of natural mutation of the beta-globin gene (HBB) affecting the gametes and transferred to subsequent generations. Using restriction fragment length polymorphism analysis, four main African haplotypes and one Asian haplotype of the beta-globin chain genes have been characterized and are believed to originate differently in these regions. The main African haplotypes include Senegal, Benin, Bantu (central-African republic), and Cameroon haplotype . The Bantu haplotype is associated with the most severe disease phenotype while the Asian (also called Arab-Indian) haplotype is associated with a mild phenotype .SCD is found in other parts of the world including USA and Europe due to migration and interracial marriages . The high prevalence of SCD in sub-Saharan Africa has been attributed to survival advantage conferred by the sickle cell trait against *Plasmodium falciparum*. Resistance of individuals with sickle cell trait to *Plasmodium falciparum* creates a selective pressure that has maintained the sickle cell gene within human populations in malaria endemic regions like sub-Saharan Africa. This phenomenon is termed balanced polymorphism

## The predominant presentations were bone pain in 97 (74%), nephropathy in 47 (35.9%) and pathological fractures in 58 (44.3%). Sixty-seven percent (67%) of the patients were less than 60 years, and 35% had Bence Jones proteinuria. The overall survival beyond 6 months was 91.3%, mean duration of survival rate was 7.4 months. Majority (66.2%) were on Melphalan alone or on melphalan-containing combinations. A higher packed cell volume (PCV) and total serum protein levels at presentation were associated with increased survival, p=0.033 and 0.036, respectively.

REFERENCE

[Understanding Non Cancerous Blood Disorders - Acibadem Health Point - ACIBADEM Hospitals - Acibadem Health Group](https://www.acibademhealthpoint.com/understanding-non-cancerous-blood-disorders/)

<https://my.clevelandclinic.org/health/diseases/21545-blood-disorders>

<https://pmc.ncbi.nlm.nih.gov/articles/PMC4312619/#sec2>

**BONE MARROW FAILURE**

### DEFINITION AND DESCRIPTION

Bone marrow failure happens when your bone marrow doesn’t produce enough of the red blood cells, white blood cells or platelets that help keep your body working. Platelets help your blood to clot. Red blood cells carry oxygen throughout your body. White blood cells fight infection.

Bone marrow failure usually is a complication of other medical conditions, but it can also happen for no known reason. Healthcare providers can treat bone marrow failure with medication and procedures that temporarily ease symptoms, but an allogeneic stem cell transplant is the only long-term term treatment for bone marrow failure.

#### Types of bone marrow failure

There are two types of bone marrow failure:

* Acquired: Experts don’t know all the reasons why people develop acquired bone marrow failure. But research shows the condition may happen from having certain diseases or being exposed to certain chemicals or medications. Acquired bone marrow failure develops over time.
* Inherited: This type may happen if you inherit gene changes (mutations) from one or both of your biological parents. Healthcare providers call this bone marrow failure syndrome.

## Symptoms

Symptoms vary depending on what’s causing the bone marrow failure. For example, people with inherited bone marrow failure may start showing symptoms at age 2. But research shows that people with an acquired form of the condition may have symptoms that appear between ages 20 and 25 or after age 65. Regardless of when they start, the most common bone marrow failure symptoms are:

* Bone pain
* Excessive bleeding
* Fatigue
* Fever
* Frequent bacterial infections
* Headaches
* Shortness of breath (dyspnea)
* Skin color that’s paler than usual
* Tiny spots of blood under your skin (petechiae)
* Unexplained bruising

### 

### causes of bone marrow failure

You may develop bone marrow failure if:

* You have bone marrow failure syndrome.
* You have blood cancer, blood disorders or develop certain types of blood disorders, cancer or infections (acquired bone marrow failure).
* You’re exposed to chemicals, drugs and medication that increase your risk (acquired bone marrow failure).

Sometimes, the condition happens for no known reason. Healthcare providers may call this “idiopathic bone marrow failure.” Researchers believe there’s a connection between autoimmunity and bone marrow failure. Autoimmunity is when your immune system mistakenly targets your bone marrow.

#### 

#### Bone marrow failure syndromes

These are inherited conditions with related or similar signs or symptoms:

* Congenital agranulocytosis (Kostmann syndrome): This condition affects your neutrophils, a type of white blood cell.
* Congenital amegakaryocytic thrombocytopenia (CAMT): In this condition, you have fewer megakaryocytes, which are bone marrow cells that help to make platelets.
* Diamond-Blackfan anemia: This is a chronic condition that affects red blood cell production.
* Dyskeratosis congenita: Symptoms of this condition include skin changes that are an early symptom of bone marrow failure.
* Fanconi anemia: This is the most common bone marrow failure syndrome.
* Reticular dysgenesis: This is a form of severe combined immunodeficiency (SCID), when your body doesn’t make enough mature T-cells.
* Severe congenital neutropenia: In this condition, you have a lower-than-usual number of neutrophils, a type of white blood cell.
* Shwachman-Diamond syndrome: This condition affects your pancreas, bone marrow and bones.

If one of your biological parents has the condition and symptoms of the condition (autosomal dominant), there’s a 50% chance you’ll develop that condition and have an increased risk of bone marrow failure syndrome.

Your risk of bone marrow failure drops to 25% if both of your biological parents carry a genetic mutation for the same type of bone marrow failure syndrome but neither has the condition (autosomal recessive).

#### Blood cancers

You have increased risk of bone marrow failure if you have one of the following:

* Lymphoma
* Multiple myeloma
* Myelodysplastic syndrome

#### Blood disorders

Some people are born with these conditions. Others develop them over time. They include:

* Aplastic anemia: This rare blood disorder damages your bone marrow so it can’t make new blood cells and platelets. Healthcare providers may use the term “aplastic anemia” when they talk about bone marrow failure.
* Cytopenias: This includes cytopenias like autoimmune neutropenia, idiopathic neutropenia and large granular lymphocyte leukemia.
* Paroxysmal nocturnal hemoglobinuria: In this condition, your immune system breaks down red blood cells.
* Pure red cell aplasia: This is another inherited condition that affects red blood cell production.

#### Viral infections

The following viral infections may increase your risk:

* Cytomegalovirus
* Epstein-Barr virus
* Human immunodeficiency virus (HIV)
* Parvovirus B19
* Viral hepatitis

Chemotherapy and/or radiation therapy for cancer may increase your risk of developing bone marrow failure. Likewise, exposure to chemicals and solvents used in some insecticides and pesticides may increase your risk.

### 

### complications of bone marrow failure

It can be life-threatening and may also cause the following complications, even after treatment:

* Bacterial or viral infections
* Bleeding
* Blood cancers, like acute myeloid leukemia or myelodysplasia
* Cancerous tumors like osteosarcoma and rhabdomyosarcoma
* Squamous cell carcinoma

## 

## Diagnosis and Tests

A healthcare provider will first ask about your symptoms, your medical history and your family medical history. They’ll also do a physical exam. They may do blood tests and imaging tests as well.

#### Blood tests

Blood tests may include:

* Ceruloplasmin test
* Complete blood count (CBC)
* Ferritin test
* Folate deficiency test
* Vitamin B12 deficiency

#### Imaging tests

Imaging tests may include:

* Magnetic resonance imaging (MRI)scan
* Positron emission tomography (PET) scan
* Ultrasound

Depending on the results of blood and imaging tests, your provider may do a bone marrow biopsy. They may recommend genetic testing that would detect mutations that cause bone marrow failure.

Your provider may also do tests for certain infections or to rule out other conditions. Your provider will explain why they’re doing each test and what the tests may show.

## 

## Management and Treatment

Your treatment will depend on factors, including:

* The type of bone marrow failure, including whether it’s inherited or acquired.
* The severity of your situation.
* Your age and overall health.
* Your symptoms.

Treatments may include:

* Antibiotics, antifungal and antiviral medication, to fight infection
* Blood transfusion, to increase red blood cells and ease symptoms like bleeding and fatigue
* Bone marrow stimulants, which help your bone marrow to make more blood cells
* Immunosuppressants, to help stop your immune system from attacking your bone marrow
* Allogeneic stem cell (bone marrow) transplant

#### What are treatment complications or side effects?

Complications and side effects vary depending on the treatment, but stem cell (bone marrow) transplants may cause the most significant issues, including graft vs. host disease and infection.

## Prevention

Unfortunately, you can’t reduce your risk of inherited bone marrow failure. Avoiding chemicals that are associated with bone marrow suppression may reduce your risk of developing some acquired bone marrow failure. And prompt treatment can help relieve your symptoms and improve your quality of life.

## Outlook / Prognosis

Your prognosis is what you can expect to happen after treatment, and that can depend on several different factors, including the condition type, your age and overall health, and how well your body responds to treatment.

In general, people with bone marrow failure need ongoing medical treatment and support. But everyone is different. To understand your prognosis, ask your healthcare provider about next steps after your initial treatment.

#### Is bone marrow failure a terminal illness?

It’s a very serious illness that may be life-threatening. Most people with bone marrow failure receive treatment from experienced specialists, including oncologists and hematologists.

### What is the life expectancy for someone with bone marrow failure?

Life expectancy is an estimate of how long you may live after treatment for a specific condition. Life expectancy for people with bone marrow failure can range from months to a full lifespan.

But you’re unique and your experience may be different from everyone else. Ask your healthcare provider about what you can expect, including how long you could live. They’re your best resource for information since they know you and your situation.

### How do I take care of myself?

The best way is to take care of your general health. For example, don’t use tobacco products and cut back on or stop drinking beverages that contain alcohol. Here are other suggestions:

* See your healthcare provider regularly. Bone marrow failure can be a lifelong condition. You may need ongoing treatment. It can also cause new medical issues, so it’s important that you have regular check-ups. Your provider will monitor your overall health and treat any new issues.
* Eat a healthy diet. Your symptoms and treatment side effects may affect your appetite or make it hard for you to eat. If you’re worried about getting enough nutrition, talk to a nutritionist. They’ll have recommendations.
* Get some exercise. It can be stressful to have a serious medical issue like bone marrow failure. Exercise is a good way to reduce stress. Be sure to talk to your healthcare provider before starting a new exercise routine.

## 

## Differential Diagnoses

* Acute Myeloid Leukemia (AML)
* Anemia
* Aplastic Anemia
* Hairy Cell Leukemia
* Paroxysmal Nocturnal Hemoglobinuria

## Epidemiology

## Bone marrow failure has triphasic peaks: at 2 to 5 years (inherited is most common), between 20 to 25 years, and after 65 years (most likely due to acquired causes). The incidence of inherited bone marrow failure accounts for 10% to 15% of marrow aplasia and 30% of pediatric bone marrow failure disorders, with approximately 65 cases per million live births every year. The majority of children with inherited bone marrow failures have an identifiable cause (75%). Patients can present as adults. The most common inherited bone marrow failure is Fanconi anemia which occurs in 1 to 5 cases per million with a carrier frequency of 1 in 200 to 300; however, it is more common in Spanish gypsies (1 in 64), Afrikaners in South Africa carrying a specific mutation (1 in 83), and Ashkenazi Jews (1 in 89). Ten percent of patients who present with bone marrow failure have unsuspected Fanconi anemia.

## 

## REFERENCE

[Bone Marrow Failure - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK459249/#article-18447.s4)

<https://my.clevelandclinic.org/health/diseases/24918-bone-marrow-failure>

[Bone Marrow Failure Differential Diagnoses](https://emedicine.medscape.com/article/199003-differential)

## IRON METABOLIC DISORDER

**DEFINITION AND DESCRIPTION**

Iron metabolism disorders are a group of conditions which involve an excess or deficiency of iron in the body. Iron is vital to the production of red blood cells and therefore is key to survival, but an excess of iron can cause cell damage due to oxidative stress. Proper regulation of the levels of iron in your body is therefore important.

The most common iron metabolism disorders are iron deficiency anaemia, hereditary haemochromatosis, and iron overload.

## Iron deficiency anemia is a common type of anemia — a condition in which blood lacks adequate healthy red blood cells. Red blood cells carry oxygen to the body's tissues.

## As the name implies, iron deficiency anemia is due to insufficient iron. Without enough iron, your body can't produce enough of a substance in red blood cells that enables them to carry oxygen (hemoglobin). As a result, iron deficiency anemia may leave you tired and short of breath.

## You can usually correct iron deficiency anemia with iron supplementation. Sometimes additional tests or treatments for iron deficiency anemia are necessary, especially if your doctor suspects that you're bleeding internally.

## Hemochromatosis is a metabolic disorder in which your organs accumulate excess iron, leading to organ damage. Hereditary hemochromatosis affects one in 300 people in the United States. However, it often goes undiagnosed, partially due to its nonspecific symptoms. The classic form of hemochromatosis is most common in Caucasians of Northern European descent. It is a genetic disease that may be found in families.

## Initially, iron deficiency anemia can be so mild that it goes unnoticed. But as the body becomes more deficient in iron and anemia worsens, the signs and symptoms intensify.

## Iron overload

## Iron overload is the more general term for having too much iron in your body. While haemochromatosis is iron overload caused by a genetic problem, iron overload can also occur as a result of:

## liver disease

## excessive iron intake through your diet

## regular blood transfusions, often given to patients with sickle cell disease or some types of anaemia

## In these situations, unlike haemochromatosis, there are rarely any “early warning signs” of iron overload, and many people are only diagnosed after organ damage has occurred. Treatment can include medication to reduce the iron levels in your blood, and dietary advice.

**SIGNS AND SYMPTOMS**

Iron deficiency anemia signs and symptoms may include:

Extreme fatigue

Weakness

Pale skin

Chest pain, fast heartbeat or shortness of breath

Headache, dizziness or lightheadedness

Cold hands and feet

Inflammation or soreness of your tongue

Brittle nails

Unusual cravings for non-nutritive substances, such as ice, dirt or starch

Poor appetite, especially in infants and children with iron deficiency anemia

Symptoms of hemochromatosis usually appear after age 50, once significant iron has accumulated in the body. Symptoms may appear later in women, typically about 10 years after menopause.

## Many patients with hemochromatosis do not exhibit any symptoms. The disease is usually diagnosed as a result of family screening or after a blood test indicates a high level of iron or abnormal liver enzymes. Early signs are nonspecific and may include:

## Weakness and fatigue

## Increased skin pigmentation

## Hair loss

## Impotence and loss of sex drive

## Joint pains

## Memory loss

## More specific symptoms occur when the iron accumulates in particular organs:

## Iron deposits in the heart muscle may cause an arrhythmia, or heart failure.

## Iron deposits in the liver can predispose a patient to fibrosis, cirrhosis and liver cancer.

## Iron deposits in the pancreas can cause diabetes mellitus.

## Iron deposits in the brain and gonads (ovaries and testicles) can lead to impotence.

## Patients with hemochromatosis are at increased risk for pancreatic cancer. Arthritis also can develop as a result of the excess iron.

## Causes

## Iron deficiency anemia occurs when your body doesn't have enough iron to produce hemoglobin. Hemoglobin is the part of red blood cells that gives blood its red color and enables the red blood cells to carry oxygenated blood throughout your body.

## If you aren't consuming enough iron, or if you're losing too much iron, your body can't produce enough hemoglobin, and iron deficiency anemia will eventually develop.

## Causes of iron deficiency anemia include:

## Blood loss. Blood contains iron within red blood cells. So if you lose blood, you lose some iron. Women with heavy periods are at risk of iron deficiency anemia because they lose blood during menstruation. Slow, chronic blood loss within the body — such as from a peptic ulcer, a hiatal hernia, a colon polyp or colorectal cancer — can cause iron deficiency anemia. Gastrointestinal bleeding can result from regular use of some over-the-counter pain relievers, especially aspirin.

## A lack of iron in your diet. Your body regularly gets iron from the foods you eat. If you consume too little iron, over time your body can become iron deficient. Examples of iron-rich foods include meat, eggs, leafy green vegetables and iron-fortified foods. For proper growth and development, infants and children need iron from their diets, too.

## An inability to absorb iron. Iron from food is absorbed into your bloodstream in your small intestine. An intestinal disorder, such as celiac disease, which affects your intestine's ability to absorb nutrients from digested food, can lead to iron deficiency anemia. If part of your small intestine has been bypassed or removed surgically, that may affect your ability to absorb iron and other nutrients.

## Pregnancy. Without iron supplementation, iron deficiency anemia occurs in many pregnant women because their iron stores need to serve their own increased blood volume as well as be a source of hemoglobin for the growing fetus.

## Risk factors

## These groups of people may have an increased risk of iron deficiency anemia:

## Women. Because women lose blood during menstruation, women in general are at greater risk of iron deficiency anemia.

## Infants and children. Infants, especially those who were low birth weight or born prematurely, who don't get enough iron from breast milk or formula may be at risk of iron deficiency. Children need extra iron during growth spurts. If your child isn't eating a healthy, varied diet, he or she may be at risk of anemia.

## Vegetarians. People who don't eat meat may have a greater risk of iron deficiency anemia if they don't eat other iron-rich foods.

## Frequent blood donors. People who routinely donate blood may have an increased risk of iron deficiency anemia since blood donation can deplete iron stores. Low hemoglobin related to blood donation may be a temporary problem remedied by eating more iron-rich foods. If you're told that you can't donate blood because of low hemoglobin, ask your doctor whether you should be concerned.

## Complications

## Mild iron deficiency anemia usually doesn't cause complications. However, left untreated, iron deficiency anemia can become severe and lead to health problems, including the following:

## Heart problems. Iron deficiency anemia may lead to a rapid or irregular heartbeat. Your heart must pump more blood to compensate for the lack of oxygen carried in your blood when you're anemic. This can lead to an enlarged heart or heart failure.

## Problems during pregnancy. In pregnant women, severe iron deficiency anemia has been linked to premature births and low birth weight babies. But the condition is preventable in pregnant women who receive iron supplements as part of their prenatal care.

## Growth problems. In infants and children, severe iron deficiency can lead to anemia as well as delayed growth and development. Additionally, iron deficiency anemia is associated with an increased susceptibility to infections.

## Prevention

## You can reduce your risk of iron deficiency anemia by choosing iron-rich foods.

### Choose iron-rich foods

## Foods rich in iron include:

## Red meat, pork and poultry

## Seafood

## Beans

## Dark green leafy vegetables, such as spinach

## Dried fruit, such as raisins and apricots

## Iron-fortified cereals, breads and pastas

## Peas

## Your body absorbs more iron from meat than it does from other sources. If you choose to not eat meat, you may need to increase your intake of iron-rich, plant-based foods to absorb the same amount of iron as does someone who eats meat.

### Choose foods containing vitamin C to enhance iron absorption

## You can enhance your body's absorption of iron by drinking citrus juice or eating other foods rich in vitamin C at the same time that you eat high-iron foods. Vitamin C in citrus juices, like orange juice, helps your body to better absorb dietary iron.

## Vitamin C is also found in:

## Broccoli

## Grapefruit

## Kiwi

## Leafy greens

## Melons

## Oranges

## Peppers

## Strawberries

## Tangerines

## Tomatoes

### Preventing iron deficiency anemia in infants

## To prevent iron deficiency anemia in infants, feed your baby breast milk or iron-fortified formula for the first year. Cow's milk isn't a good source of iron for babies and isn't recommended for infants under 1 year. After age 6 months, start feeding your baby iron-fortified cereals or pureed meats at least twice a day to boost iron intake. After one year, be sure children don't drink more than 20 ounces (591 milliliters) of milk a day. Too much milk often takes the place of other foods, including those that are rich in iron.

## 

## 

## Diagnosis and test

To diagnose iron deficiency anemia, your doctor may run tests to look for:

* **Red blood cell size and color.** With iron deficiency anemia, red blood cells are smaller and paler in color than normal.
* **Hematocrit.** This is the percentage of your blood volume made up by red blood cells. Normal levels are generally between 35.5 and 44.9 percent for adult women and 38.3 to 48.6 percent for adult men. These values may change depending on your age.
* **Hemoglobin.** Lower than normal hemoglobin levels indicate anemia. The normal hemoglobin range is generally defined as 13.2 to 16.6 grams (g) of hemoglobin per deciliter (dL) of blood for men and 11.6 to 15 grams (g) of hemoglobin per deciliter (dL) of blood for women.
* **Ferritin.** This protein helps store iron in your body, and a low level of ferritin usually indicates a low level of stored iron.

### 

### Additional diagnostic tests

If your blood work indicates iron deficiency anemia, your doctor may order additional tests to identify an underlying cause, such as:

* **Endoscopy.** Doctors often check for bleeding from a hiatal hernia, an ulcer or the stomach with the aid of endoscopy. In this procedure, a thin, lighted tube equipped with a video camera is passed down your throat to your stomach. This allows your doctor to view the tube that runs from your mouth to your stomach (esophagus) and your stomach to look for sources of bleeding.
* **Colonoscopy.** To rule out lower intestinal sources of bleeding, your doctor may recommend a procedure called a colonoscopy. A thin, flexible tube equipped with a video camera is inserted into the rectum and guided to your colon. You're usually sedated during this test. A colonoscopy allows your doctor to view inside some or all of your colon and rectum to look for internal bleeding.
* **Ultrasound.** Women may also have a pelvic ultrasound to look for the cause of excess menstrual bleeding, such as uterine fibroids.

Your doctor may order these or other tests after a trial period of treatment with iron supplementation.

Treatment

To treat iron deficiency anemia, your doctor may recommend that you take iron supplements. Your doctor will also treat the underlying cause of your iron deficiency, if necessary.

### 

### Iron supplements

Your doctor may recommend over-the-counter iron tablets to replenish the iron stores in your body. Your doctor will let you know the correct dose for you. Iron is also available in liquid form for infants and children. To improve the chances that your body will absorb the iron in the tablets, you may be instructed to:

* **Take iron tablets on an empty stomach.** If possible, take your iron tablets when your stomach is empty. However, because iron tablets can upset your stomach, you may need to take your iron tablets with meals.
* **Don't take iron with antacids.** Medications that immediately relieve heartburn symptoms can interfere with the absorption of iron. Take iron two hours before or four hours after you take antacids.
* **Take iron tablets with vitamin C.** Vitamin C improves the absorption of iron. Your doctor might recommend taking your iron tablets with a glass of orange juice or with a vitamin C supplement.

Iron supplements can cause constipation, so your doctor may also recommend a stool softener. Iron may turn your stools black, which is a harmless side effect.

Iron deficiency can't be corrected overnight. You may need to take iron supplements for several months or longer to replenish your iron reserves. Generally, you'll start to feel better after a week or so of treatment. Ask your doctor when to have your blood rechecked to measure your iron levels. To be sure that your iron reserves are replenished, you may need to take iron supplements for a year or more.

### 

### Treating underlying causes of iron deficiency

If iron supplements don't increase your blood-iron levels, it's likely the anemia is due to a source of bleeding or an iron-absorption problem that your doctor will need to investigate and treat. Depending on the cause, iron deficiency anemia treatment may involve:

* Medications, such as oral contraceptives to lighten heavy menstrual flow
* Antibiotics and other medications to treat peptic ulcers
* Surgery to remove a bleeding polyp, a tumor or a fibroid

If iron deficiency anemia is severe, you may need iron given intravenously or you may need blood transfusions to help replace iron and hemoglobin quickly.

**WHEN TO SEE A DOCTOR**

Make an appointment with your doctor if you have any signs and symptoms that worry you. If you're diagnosed with iron deficiency anemia, you may need tests to look for a source of blood loss, including tests to examine your gastrointestinal tract.

Here's some information to help you get ready for your appointment, and what to expect from your doctor.

### What you can do

* **Write down any symptoms you're experiencing,** including any that may seem unrelated to the reason for which you scheduled the appointment.
* **Write down key personal information,** including any major stresses or recent life changes.
* **Make a list of all medications,** vitamins or supplements you're taking.
* **Write down questions to ask** your doctor.

Your time with your doctor is limited, so preparing a list of questions will help you make the most of your time together.

References

<https://www.mayoclinic.org/diseases-conditions/iron-deficiency-anemia/diagnosis-treatment/drc-20355040>

## <https://www.mayoclinic.org/diseases-conditions/iron-deficiency-anemia/symptoms-causes/syc-20355034>

<https://www.topdoctors.co.uk/medical-dictionary/disorder-of-iron-metabolism/>

# 

# 

# Thalassemias

# Other Names for Thalassemias

## The various types of thalassemia have specific names related to the severity of the disorder.

## Alpha Thalassemias

## Alpha thalassemia silent carrier

## Alpha thalassemia minor, also called alpha thalassemia trait

## Hemoglobin H disease

## Alpha thalassemia major, also called hydrops fetalis

## Beta Thalassemias

## Beta thalassemia minor, also called beta thalassemia trait

## Beta thalassemia intermedia

## Beta thalassemia major, also called Cooley's anemia or beta-zero (ß0) thalassemia

## Beta-plus (ß+) thalassemia

## Mediterranean anemia

## DEFINITION AND DESCRIPTION

## Thalassemia (thal-uh-SEE-me-uh) is a blood disorder. It's inherited, which means it's passed from parents to children through genes. Genes carry information that can affect many things, including what people look like and whether they might have certain diseases.

## Thalassemia causes the body to have less of the protein hemoglobin than usual. Hemoglobin is present in red blood cells and allows the red blood cells to carry oxygen. Not having enough hemoglobin or red blood cells can lead to a condition called anemia. That can make you feel tired and weak.

## If you have a mild form of thalassemia called thalassemia trait, you do not need any specific treatment. But with more-serious forms, you might need regular blood transfusions. Those are treatments in which you receive blood from a donor. Lifestyle changes also are key. For instance, a healthy diet and regular exercise can help you manage tiredness.

## Symptoms

## There are different types of thalassemia. The symptoms that you have depend on the type and how serious it is.

## Symptoms of severe thalassemia can include:

## Tiredness, also called fatigue.

## Weakness.

## A change in skin color or a yellowing of skin and eyes.

## Changes or problems with facial bones.

## Slow growth.

## Swelling of the stomach area, also called the abdomen.

## Dark urine.

## Poor appetite.

## Some babies show symptoms of thalassemia at birth. Others get symptoms during the first two years of life. But some people with thalassemia don't have symptoms

## Causes

## Thalassemia is caused by gene changes in cells that make hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen throughout the body. The gene changes linked with thalassemia are passed from parents to children.

## Hemoglobin molecules are made of protein chains called alpha and beta chains. These chains are affected by gene changes. With thalassemia, the body doesn't make enough of either the alpha or the beta chains. That causes you to get either alpha-thalassemia or beta-thalassemia, the two main types of the condition.

## In beta-thalassemia, the gene change is an alteration in the DNA. Other terms used to describe these changes include mutation or variation. In alpha-thalassemia, the altered DNA consists of missing one or more copies of the four genes that program the alpha chain. This also is termed "deletion."

## With alpha-thalassemia, the seriousness of the condition depends on the number of missing genes you inherit from your parents. The more missing copies of the genes, the worse your thalassemia.

## With beta-thalassemia, the seriousness of the condition depends on which part of the hemoglobin molecule is affected.

### Alpha-thalassemia

## Four genes are involved in making the alpha hemoglobin chain. You get two from each of your parents. The seriousness of alpha-thalassemia depends on how many copies of the genes are missing:

## If one copy of the gene is missing, you'll have no symptoms of thalassemia. But you carry the disease and can pass it on to your children.

## If two copies of the genes are missing, your thalassemia symptoms likely will be mild. You might hear this condition called alpha-thalassemia trait.

## If three copies of the genes are missing, your symptoms likely will be moderate to severe.

## It's rare to be missing all four copies of the genes. It usually leads to stillbirth. That's the loss of a pregnancy at or after 20 weeks. Babies born with four missing genes often die shortly after birth. Or they need blood transfusions for the rest of their lives. Sometimes, a child born with this condition can be treated with blood transfusions and a stem cell transplant.

### Beta-thalassemia

## Two genes are involved in making the beta hemoglobin chain. You get one from each of your parents. Unlike the missing genes that cause alpha-thalassemia, small changes in the gene cause beta-thalassemia. These changes lead to reduced production of the beta chain. If you inherit:

## One gene with changes, you'll usually have mild symptoms. This condition is called non transfusion-dependent thalassemia. If you have no symptoms, you may hear your condition called beta-thalassemia trait or thalassemia minor.

## Two genes with changes, your symptoms typically will be moderate to severe. This condition is called transfusion-dependent beta-thalassemia or thalassemia major. Babies born with two changed beta hemoglobin genes usually are healthy at birth. They often get symptoms within the first two years of life. But it is possible to get a milder form of the disease with two changed genes.

## Risk factors

## Factors that raise your risk of thalassemia include:

## Family history of thalassemia. The condition passed from parents to children through genetic changes in hemoglobin genes.

## Certain ancestry. Thalassemia happens most often in people of South Asian, Italian, Greek, Middle Eastern or African descent.

## Complications

## Health problems that can stem from moderate to severe thalassemia include:

## Iron overload. People with thalassemia can get too much iron in their bodies. This can be due to the disease or to frequent blood transfusions. Too much iron can result in damage to the heart, liver, and glands that make and release hormones.

## Infection. People with thalassemia have a higher risk of infections. This is especially true if they've had their spleens removed.

## Severe thalassemia can lead to the following health problems:

## Bone changes. Thalassemia can cause the spongy tissue inside some bones, called bone marrow, to expand. That makes bones widen. It can lead to an irregular bone structure, especially in the face and skull. Expanding bone marrow also makes bones thin and brittle. That raises the chance of broken bones.

## Enlarged spleen. The spleen is an organ that helps the body fight infection. It also helps remove old or damaged blood cells. Often, thalassemia happens along with the destruction of a large number of red blood cells. This causes the spleen to get bigger and work harder than usual. An enlarged spleen can make anemia worse. It also can reduce the life of red blood cells received in a transfusion. If your spleen grows too big, your health care professional might recommend surgery to remove it.

## Slowed growth rates. Anemia can slow a child's growth and delay puberty.

## Heart problems. Congestive heart failure and irregular heart rhythms can be linked with severe thalassemia.

## Prevention

## Most of the time, you can't prevent thalassemia. If you have the condition or if you have the thalassemia gene changes that cause it, it is very important to talk with a genetic counselor. The counselor can offer advice on the risks of your children being affected.

## Some people with thalassemia major think about getting pregnant with assisted reproductive technology. This includes procedures such as in vitro fertilization. IVF joins an egg and a sperm outside the body to make the earliest stage of an unborn baby, called an embryo. An exam called preimplantation genetic testing can then be used to check the embryo for gene changes related to thalassemia. If an embryo doesn't have these changes, it can be placed in the uterus to start a pregnancy. This might help people who have thalassemia or a related gene have healthy babies.

## Another procedure that might lead to pregnancy is called intrauterine insemination. Sperm from a donor who doesn't have thalassemia or the genes related to the condition is placed in the uterus to join with an egg.

## 

## Diagnosis

Most children with moderate to severe thalassemia show symptoms within their first two years of life. If your child's health care professional thinks your child might have thalassemia, blood tests can confirm it.

Blood tests can reveal the number of red blood cells and irregular changes in their size, shape or color. Blood tests also can be used to look for gene changes in DNA.

### Prenatal testing

Testing can be done before a baby is born to find out if the baby has thalassemia. Testing also can determine how serious the condition might be. Tests used to find thalassemia in unborn babies include:

* Chorionic villus sampling. This test involves removing a tiny piece of the placenta. The placenta is the organ that forms during pregnancy to give a baby oxygen and nutrients in the womb. Once removed, the placenta sample is checked by a lab. Most often, it's done around the 11th week of pregnancy.
* Amniocentesis. This test involves checking a sample of the fluid that surrounds the unborn baby in the womb. The test usually is done around the 16th week of pregnancy.

**Treatment**

Mild forms of thalassemia trait don't need treatment.

For moderate to severe thalassemia, treatments might include:

* **Frequent blood transfusions.** It's common to need these. Some people need them as often as every few weeks. Over time, blood transfusions cause a buildup of iron in blood. That can damage the heart, liver and other organs.
* **Chelation therapy.** This treatment removes extra iron from the blood. Iron can build up due to regular transfusions. Some people with thalassemia who don't have regular transfusions also can develop excess iron. Removing the excess iron is vital for your health.  
  To help rid your body of the extra iron, you might need to take medicine by mouth. The medicines include deferasirox (Exjade, Jadenu) or deferiprone (Ferriprox). Another drug called deferoxamine (Desferal) is given through a needle in a vein.
* **Other medicines.** A medicine given by shot called luspatercept (Reblozyl) helps some people need fewer blood transfusions. A medicine taken by mouth called hydroxyurea (Hydrea, Droxia) can lower the chances of getting other health problems because of thalassemia.
* **Stem cell transplant.** This also is called a bone marrow transplant. Sometimes, it might be a treatment option. For children with severe thalassemia, it can get rid of the need for lifelong blood transfusions and drugs to control iron overload.  
  A stem cell transplant involves receiving infusions of stem cells from a donor with matching cells, often a healthy sibling.

**Self care**

Follow your thalassemia treatment plan and practice these healthy habits.

* **Do not take in extra iron.** Don't take vitamins or other supplements that contain iron unless your health care professional recommends them. Also, ask if you should limit foods that have lots of iron. These include meat, fish, spinach, and some cereals and orange juices.
* **Eat a healthy diet.** Healthy eating can help you feel better and boost your energy. Your health care professional also might recommend a folic acid supplement. This helps your body make new red blood cells.  
  To keep your bones healthy, make sure you get enough calcium and vitamin D. Ask your health care team what the right amounts are for you and whether you need a supplement.
* **Lower your risk of infections.** Wash your hands often, and stay away from sick people. This is key, especially if you've had your spleen removed.  
  Stay up to date on your flu and COVID-19 vaccines too. Also get vaccines to prevent meningitis, pneumonia and hepatitis B. If you run a fever or have other symptoms of an infection, see your health care professional for treatment.
* **Get regular exercise.** If you're not active now, ask your health care team to help you get started. You might be told to try heart-healthy aerobic exercises such as walking, biking or jogging. If you have joint pain, you could try gentle activities such as yoga, swimming or water aerobics.

## 

## Differential Diagnoses

* Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency
* Iron Deficiency Anemia
* Sideroblastic Anemias

# Living with Thalassemias

Survival and quality of life have improved for people who have moderate or severe thalassemias. This is because:

* More people are able to get blood transfusions now.
* Blood screening has reduced the number of infections from blood transfusions. Also, treatments for other kinds of infections have improved.
* Iron chelation treatments are available that are easier for some people to take.
* Some people have been cured through blood and marrow stem cell transplants.

Living with thalassemia can be challenging, but several approaches can help you cope.

## Follow Your Treatment Plan

Following the treatment plan your doctor gives you is important. For example, get blood transfusions as your doctor recommends, and take your iron chelation medicine as prescribed.

Iron chelation treatment can take time and be mildly painful. However, don't stop taking your medicine. The leading cause of death among people who have thalassemias is heart disease caused by iron overload. Iron buildup can damage your heart, liver, and other organs.

Several chelation treatments are now available, including injections and pills. Your doctor will talk with you about which treatment is best for you.

Take folic acid supplements if your doctor prescribes them. Folic acid is a B vitamin that helps build healthy red blood cells. Also, talk with your doctor about whether you need other vitamin or mineral supplements, such as vitamins A, C, or D or selenium.

## Get Ongoing Medical Care

Keep your scheduled medical appointments, and get any tests that your doctor recommends.

These tests may include:

* Monthly complete blood counts and tests for blood iron levels every 3 months
* Yearly tests for heart function, liver function, and viral infections (for example, hepatitis B and C and HIV)
* Yearly tests to check for iron buildup in your liver
* Yearly vision and hearing tests
* Regular checkups to make sure blood transfusions are working
* Other tests as needed (such as [lung function tests](https://www.nhlbi.nih.gov/health/health-topics/topics/lft/), genetic tests, and tests to match your tissues with a possible donor if a stem cell transplant is being considered)

Children who have thalassemias should receive yearly checkups to monitor their growth and development. The checkups include a physical exam, including a height and weight check, and any necessary tests.

**Take Steps To Stay Healthy**

Take steps to stay as healthy as possible. Follow a healthy eating plan and your doctor's instructions for taking iron supplements.

Get vaccinations as needed, especially if you've had your spleen removed. You may need vaccines for the flu, [pneumonia](https://www.nhlbi.nih.gov/health/health-topics/topics/pnu/), hepatitis B, and meningitis. Your doctor will advise you about which vaccines you need.

Watch for signs of infection (such as a fever) and take steps to lower your risk for infection (especially if you've had your spleen removed). For example:

* Wash your hands often.
* Avoid crowds during cold and flu season.
* Keep the skin around the site where you get blood transfusions as clean as possible.
* Call your doctor if a fever develops.

**REFERENCE**

[Signs, Symptoms, and Complications of Thalassemias | Hematology-Oncology Associates of CNY](https://www.hoacny.com/patient-resources/blood-disorders/what-thalassemias/signs-symptoms-and-complications-thalassemias)

[Thalassemia Intermedia Differential Diagnoses](https://emedicine.medscape.com/article/959122-differential?form=fpf)

[Thalassemia - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/thalassemia/diagnosis-treatment/drc-20355001)

## [Thalassemia - Symptoms & causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/thalassemia/symptoms-causes/syc-20354995)

# 

# 

# 

# Bleeding disorders

## Alternative Names

Coagulopathy

**DEFINITION AND DESCRIPTION**

Bleeding disorders are a group of conditions in which there is a problem with the body's blood clotting process. These disorders can lead to heavy and prolonged bleeding after an injury or surgery. Bleeding can also begin on its own and may be difficult to stop.

Specific bleeding disorders include:

* Acquired platelet function defects
* Congenital platelet function defects
* Disseminated intravascular coagulation (DIC)
* Prothrombin deficiency
* Factor V deficiency
* Factor VII deficiency
* Factor X deficiency
* Factor XI deficiency (hemophilia C)
* Glanzmann disease
* Hemophilia A
* Hemophilia B
* Idiopathic thrombocytopenic purpura (ITP)
* Von Willebrand disease (types I, II, and III)

## Causes

Blood clotting

Normal blood clotting involves blood particles, called platelets, and as many as 20 different plasma proteins that layer over the platelets. These proteins are known as blood clotting or coagulation factors. These factors interact with other chemicals to form a substance called fibrin that stops bleeding.

Problems can occur when platelets are low in number or do not work properly or when certain coagulation factors are low or missing. Bleeding problems can range from mild to severe.

Some bleeding disorders are present at birth and are passed down through families (inherited). Others develop from:

* Illnesses, such as vitamin K deficiency or severe liver disease
* Treatments, such as the use of drugs to stop blood clots (anticoagulants) or the long-term use of antibiotics

Bleeding disorders can also result from a problem with the number or function of platelets. These disorders can also be either inherited or developed later (acquired). The side effects of certain drugs often lead to the acquired forms.

## Symptoms

Symptoms may include any of the following:

* Bleeding into joints or muscles
* Bruising easily
* Heavy bleeding
* Heavy menstrual bleeding
* Nosebleeds that do not stop easily
* Excessive bleeding with surgical procedures
* Umbilical cord bleeding after birth

The problems that occur depend on the specific bleeding disorder, and how severe it is.

## Diagnosis and Tests

Tests that may be done include:

* Complete blood count (CBC)
* Partial thromboplastin time (PTT)
* Platelet aggregation test
* Prothrombin time (PT)
* Mixing study, a special PTT test to confirm the factor deficiency

## Treatment

Treatment depends on the type of disorder. It may include:

* Clotting factor replacement
* Fresh frozen plasma transfusion
* Platelet transfusion
* Other treatments

## Outlook (Prognosis)

Outcome also depends on the disorder. Most primary bleeding disorders can be managed. When the disorder is due to diseases, such as DIC, the outcome will depend on how well the underlying disease can be treated.

## Possible Complications

Complications may include:

* Bleeding in the brain
* Severe bleeding (usually from the gastrointestinal tract or injuries)

Other complications can occur, depending on the disorder.

## When to see a doctor

Contact your health care provider if you notice any unusual or severe bleeding.

## Prevention

Prevention depends on the specific disorder.

**Differential Diagnosis**

* Malignancy
* Severe liver failure
* Thrombocytopenia
* Vitamin K deficiency
* Antithrombin III deficiency
* Massive transfusion
* Disseminated intravascular coagulation
* Lupus anticoagulant
* Protein C deficiency
* Protein S deficiency
* Idiopathic thrombocytopenic purpura (ITP)
* Medication side effects

**EPIDEMIOLOGY**

Hereditary bleeding disorders are due to the absence or deficiency of specific clotting proteins which act as procoagulants through precise interactions in the clotting cascade. The three most common are hemophilia A (Factor VIII deficiency), hemophilia B (Factor IX deficiency) and von Willebrand disease. Hemophilia A is an X-linked recessive genetic disorder affecting 1 in 5000 males making it the most common congenital coagulopathy. Hemophilia B is an X-linked genetic coagulopathy affecting 1 in 30000 male births. Hemophilia B is also known as Christmas disease. The origin of its namesake is from Steven Christmas, the first patient diagnosed with Hemophilia B in 1952. Since hemophilia is genetic, its prevalence increases in populations in which higher levels of consanguinity exist. Females may be asymptomatic carriers of the hemophilia gene or may be found to have a partial deficiency of the specific factors involved. Von Willebrand disease is an autosomal dominant trait with no predilection for sex; however, women are more likely to exhibit symptoms as a result of increased bleeding during menstruation. Von Willebrand disease was first described in 1926 by Finnish physician Erik Adolf von Willebrand. According to the CDC, von Willebrand disease affects approximately 1% of the general population.

REFERENCES

[Bleeding Disorders - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK541050/#article-18367.s9)

[Bleeding disorders: MedlinePlus Medical Encyclopedia](https://medlineplus.gov/ency/article/001304.htm)

### 

### 

### Hamartoma

**DEFINITION AND DESCRIPTION**

A hamartoma is a benign (noncancerous) growth, or mass, that contains the same types of cells located in the part of your body where the growth forms. Unlike cells in the surrounding tissue, the cells that make up a hamartoma grow in a disorganized way. These cells clump together to form an abnormal — but harmless — tumor-like mass.

Hamartoma (pronounced “HA-mar-TOH-muh”) comes from two Greek words:

* “Hamartia,” which means a flaw or defect.
* “Oma,” which means a tumor.

Think of a hamartoma as a specific type of benign (noncancerous) tumor. A tumor is a solid mass that forms when a group of abnormal cells clumps together. Tumors can be benign or malignant (cancerous). The defining feature of a hamartoma is that the cells that clump are the same as the cells found in the surrounding normal tissue. The normal cells in a hamartoma grow together atypically.

### Where do hamartomas form in the body?

Hamartomas can form anywhere in your body. The most common locations include:

* Lungs: This is the most common site for hamartomas to form. Approximately 10% of all benign lung nodules (growths) are hamartomas.
* Skin: Skin hamartomas most often appear on your head and neck, especially your face, lips and around your ears.
* Heart: A cardiac rhabdomyoma is a rare hamartoma most commonly diagnosed during gestation (while a fetus is in the uterus) or in infancy. Although they’re rare overall, they’re the most common pediatric heart tumor.
* Brain: Hypothalamic hamartomas grow in your hypothalamus, a part of your brain that keeps essential body processes stable and in balance. They’re present at birth and usually diagnosed in childhood and adolescence. Hypothalamic hamartomas can cause symptoms, such as seizures, vision problems and precocious (early) puberty.
* Breast: About 5% of benign breast lumps are hamartomas. They’re most common in women over 35 years old.

Hamartomas associated with certain conditions, like PTEN hamartoma tumor syndrome (PHTS), may also form in your kidneys, spleen, thyroid gland, bones or other body parts.

#### Do hamartomas spread?

Hamartomas don’t spread. Unlike malignant tumors, which can spread throughout your body and damage important body structures, hamartomas stay in the place where they formed. They can cause damage if they grow so large that they impact a nearby organ or healthy tissue, but this is rare.

#### conditions associated with hamartomas

Several rare genetic conditions are associated with hamartomas. With these conditions, mutations (changes) in a gene can lead to hamartoma growth.

* Pallister-Hall syndrome (PHS): PHS is associated with mutations on the *GLI3* gene. About 5% of people with hypothalamic hamartomas also have PHS.
* Tuberous sclerosis: Tuberous sclerosis can cause hamartomas to form in various organs and body systems, including your brain, heart, kidneys, skin and eyes.
* Neurofibromatosis Type 1 (NF1): NF1 is a rare genetic condition that can cause hamartomas to grow on nerves throughout your body.
* PTEN hamartoma tumor syndrome (PHTS): PHTS is a group of syndromes that involve a mutation on the *PTEN* gene. Subtypes include Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS). Hamartomas can form in various organs and affect various body systems, including your breasts, uterus, thyroid, GI tract and skin.
* Peutz-Jeghers syndrome (PJS): PJS is associated with a mutation on the *STK11/LKB1* gene. With PJS you’re at increased risk of developing hamartomas in your lungs, stomach, bladder, small intestine, colon and rectum.

#### types of hamartomas

There are multiple types of hamartomas. Hamartomas include hypothalamic hamartomas, polyps (as in Peutz-Jeghers syndrome), cardiac rhabdomyomas, biliary duct hamartomas and retinal astrocytic hamartomas, among others. Hamartomas can grow anywhere in your body.

## Symptoms and Causes

Most hamartomas are asymptomatic, which means they don’t cause symptoms. When they do cause symptoms, it’s usually because the hamartoma has grown into nearby tissue. If you do have symptoms, they’ll usually relate to the part of your body where the hamartoma has grown.

### causes OF hamartomas

Scientists don’t know what causes hamartomas in all instances. Genetic conditions associated with hamartomas tend to be inherited. Most involve inheriting a genetic mutation from one of your biological parents.

Your healthcare provider may recommend genetic testing or counseling if you have a syndrome that’s related to hamartomas, like PHTS.

### complications of hamartomas

Most hamartomas aren’t serious. Still, they can cause problems if they grow so large that they damage an organ or body structure. For example, cardiac rhabdomyomas can lead to heart problems and even heart failure if they interfere with how your heart functions. A hypothalamic hamartoma can cause hormone imbalances, cognitive dysfunction and other symptoms if it interferes with your hypothalamus’s ability to coordinate important processes in your body.

Your healthcare provider can monitor or remove a hamartoma if they’re concerned it may cause complications.

## Diagnosis and Tests

As most hamartomas are asymptomatic, healthcare providers usually find them during imaging for an unrelated issue. Diagnosing a hamartoma can be challenging depending on where it’s located in your body because it may resemble cancerous masses.

Your provider will perform a physical exam and ask you about your medical history to help determine whether a mass is a hamartoma. Often, you’ll need additional imaging to be sure.

#### tests to be done to diagnose a hamartoma

Diagnostic tests include:

* X-ray: Uses low doses of radiation to take pictures of bones and soft tissues. Lung hamartomas sometimes have a “popcorn” like appearance on X-rays that distinguish them from cancerous masses.
* Ultrasound: Uses sound waves to generate images of soft tissue inside your body.
* Computed tomography (CT) scan: Takes multiple X-rays of soft tissue and bones inside your body. CT scans are especially useful in diagnosing lung hamartomas.
* Magnetic resonance imaging (MRI): Uses a large magnet and radio waves to create detailed images of soft tissue inside your body.
* Mammogram: Uses low doses of radiation to show the tissue inside your breast. Most breast hamartomas appear during mammograms to screen for cancer.
* Biopsy: Involves a provider removing part of the mass. A different provider called a pathologist views the cells underneath a microscope. Biopsies help determine whether a growth is made of benign cells, as in a hamartoma, or cancer cells.

## Management and Treatment

Treatment will depend on where the mass is located and whether you’re experiencing symptoms. If it’s not causing issues, your healthcare provider may choose to monitor it instead of treating it. If it’s causing symptoms or if your provider is unable to rule out cancer, surgery is the most common treatment.

#### What specific procedures are used to treat hamartomas?

Surgeries used to remove lung hamartomas include:

* Wedge resection: Removes a wedge-shaped slice of tissue, which includes the hamartoma and a small margin of surrounding normal tissue.
* Lobectomy: Removes the lobe of your lung that contains the hamartoma. The right side of your lung has three lobes. The left side has two lobes.
* Pneumonectomy: Removes your entire lung. Hamartomas are rarely serious enough to warrant this procedure.

Procedures used to remove hypothalamic hamartomas include:

* Resection surgery: A surgeon excises (removes) the tumor.
* Ablation: A surgeon uses extreme heat or a laser to destroy the tumor.
* GammaKnife® radiosurgery: A radiation oncologist directs powerful beams of energy toward your tumor, destroying it. Radiosurgery isn’t traditional surgery that involves cuts. Instead, it’s a form of radiation therapy that eliminates harmful tissue with precision, like surgery.

## Outlook / Prognosis

Most hamartomas aren’t serious. If a hamartoma is impacting an organ or has grown so large that it could cause damage, surgery usually resolves the issue. In some instances, hamartomas may be difficult to remove. For example, some hypothalamic hamartomas grow close to your optic nerve. Surgery may risk damaging it. Ask your healthcare provider if your hamartoma needs to be removed. Ask about potential complications or risks if they recommend surgery or other treatments, like radiation.

### Can a hamartoma turn cancerous?

Hamartomas can turn cancerous, but this is rare. Also, while hamartomas aren’t usually serious, conditions associated with hamartomas may increase your cancer risk. For example, Cowden syndrome, a type of PHTS, can cause hamartomas throughout your body. It also increases your risk of developing certain cancers. In this case, the hamartoma doesn’t increase your cancer risk. The condition does.

## Living With

Your healthcare provider can advise you on whether you should be concerned about a hamartoma. Questions to ask include:

* What caused the hamartoma?
* Should the hamartoma be removed?
* What symptoms will let me know that the hamartoma may need treatment?
* Is the hamartoma a sign of a more serious condition?
* Will I or anyone in my family benefit from genetic counseling or testing?

**DIFFERENTIAL DIAGNOSIS**

When encountering a possible hamartomatous lesion, the most significant consideration should be distinguishing the lesion from and excluding the possibility of underlying malignancy. Other benign pulmonary tumors should be considered upon exclusion of malignancy when deliberating the nature of a solitary pulmonary nodule, including infectious granuloma, lipoma, lipoid pneumonia, or pulmonary papilloma. Also, though 90% of these are solitary occurrences, pulmonary hamartomas can appear in association with genetic syndromes. Multiple pulmonary chondromatous hamartomas have been noted as manifestations of either the Carney triad or Cowden syndrome. The former is predominantly seen in young women and is characterized by the concurrent appearance of gastric leiomyoblastoma, pulmonary hamartoma, and extra-adrenal paraganglioma. Patients with Cowden disease often display multiple hamartomas, manifesting as mucocutaneous lesions, multiple benign tumors of internal organs, and an increased risk for several forms of cancer, including breast and digestive tract malignancies.

The differential diagnosis includes benign solid tumors that exhibit ossification or calcification, including hamartomas, pulmonary amyloidomas, and pulmonary osteomas. Hamartomas typically present as solitary lung nodules and occasionally as endobronchial tumors. Histologically, they comprise hyaline cartilage, fibromyxoid stroma, smooth muscle cells, and adipose tissues. A characteristic feature of hamartomas is the presence of mesenchymal elements and epithelial tubules (clefts) resembling bronchiolar epithelium. On CT scans, hamartomas often show fat or calcification, with calcifications present in 5% to 50% of cases and fat in up to 50%.

Nodular pulmonary amyloidosis, or amyloidoma, is a localized type of amyloid deposition in the lung parenchyma. On CT, amyloidomas appear as solitary pulmonary nodules, multiple nodular lesions, or more diffuse patterns without specific diagnostic features. The histological diagnosis is confirmed by apple-green birefringence with Congo red staining under polarized light. Pulmonary osteoma refers to a bone lesion histologically made up of lamellar bone with Haversian canals, and the term should be reserved for actual bone lesions. Osteomas appear as very dense lesions (>885 HU) on CT scans, resembling normal bone cortex, and mature osteomas may also show central marrow. A report on pulmonary osteoma appearing as a solitary pulmonary nodule on CT has been reported. However, some experts have cautiously suggested that the case reported by Markert et al may not represent a true osteoma but rather a pulmonary hamartoma with ossification.

**EPIDEMIOLOGY**

Pulmonary hamartomas occur with an incidence of 0.025% to 0.040% within the adult population.They usually present in the fifth and sixth decade of life, with men being 4 times more likely to be affected than women. Although still uncommon, these lesions are the most common benign pulmonary neoplasm, accounting for an estimated 77% of benign lung nodules and 8% of solitary lung lesions. Most hamartomas occur in the peripheral parenchyma, with exceptions observed in the central chest wall. Additionally, approximately 10% of lesions present endobronchial. Within the pediatric population, pulmonary hamartomas are significantly rarer. After adjusting for age, sex, and ethnicity, individuals with pulmonary hamartomas have a 6.3 times higher risk of developing lung cancer compared to the general population.

REFERENCE

<https://www.ncbi.nlm.nih.gov/books/NBK539806/#article-22508.s9>

[What Is a Hamartoma? Definition, Symptoms & Examples](https://my.clevelandclinic.org/health/diseases/24652-hamartoma)

**FACTOR V LEIDEN**

**DEFINITION AND DESCRIPTION**

Factor V Leiden (FAK-tur five LIDE-n) is a mutation of one of the clotting factors in the blood. This mutation can increase your chance of developing abnormal blood clots, most commonly in your legs or lungs.

Most people with factor V Leiden never develop abnormal clots. But in people who do, these abnormal clots can lead to long-term health problems or become life-threatening.

Both men and women can have factor V Leiden. Women who carry the factor V Leiden mutation may have an increased tendency to develop blood clots during pregnancy or when taking the hormone estrogen.

If you have factor V Leiden and have developed blood clots, anticoagulant medications can lessen your risk of developing additional blood clots and help you avoid potentially serious complications.

**Causes**

If you have factor V Leiden, you inherited either one copy or, rarely, two copies of the defective gene. Inheriting one copy slightly increases your risk of developing blood clots. Inheriting two copies — one from each parent — significantly increases your risk of developing blood clots.

**RISK FACTOR**

A family history of factor V Leiden increases your risk of inheriting the disorder. The disorder is most common in people who are white and of European descent.

People who have inherited factor V Leiden from only one parent have a 5 percent chance of developing an abnormal blood clot by age 65. Factors that increase this risk include:

* **Two faulty genes.** Inheriting the genetic mutation from both parents instead of just one can significantly increase your risk of abnormal blood clots.
* **Immobility.** Extended periods of immobility, such as sitting during a long airplane flight, can increase the risk of leg clots.
* **Estrogens.** Oral contraceptives, hormone replacement therapy and pregnancy can make you more likely to develop blood clots.
* **Surgeries or injuries.** Surgeries or injuries such as broken bones can increase your risk of abnormal blood clots.
* **Non-O blood type.** Abnormal blood clots are more common in people who have blood types of A, B or AB compared with those with blood type O.

**SIGNS AND SYMPTOMS**

The factor V Leiden mutation does not itself cause any symptoms. Since factor V Leiden is a risk for developing blood clots in the leg or lungs, the first indication that you have the disorder may be the development of an abnormal blood clot.

Some clots do no damage and disappear on their own. Others can be life-threatening. Symptoms of a blood clot depend on what part of your body is affected.

### A clot in a deep vein

This is known as deep vein thrombosis (DVT), which most commonly occurs in the legs. A DVT may not cause any symptoms. If signs and symptoms do occur, they can include:

* Pain
* Swelling
* Redness
* Warmth

### A clot that travels to your lungs

Known as a pulmonary embolism, this occurs when a portion of a DVT breaks free and travels through the right side of your heart to your lung, where it blocks blood flow. This can be a life-threatening situation. Signs and symptoms may include:

* Sudden shortness of breath
* Chest pain when breathing in
* A cough that produces bloody or blood-streaked sputum
* Rapid heartbeat

### DIAGNOSIS AND TEST

### Your doctor may suspect factor V Leiden if you've had one or more episodes of abnormal blood clotting or if you have a strong family history of abnormal blood clots. Your doctor can confirm that you have factor V Leiden with a blood test.

### Treatment

### Doctors generally prescribe blood-thinning medications to treat people who develop abnormal blood clots. This type of medicine usually isn't needed for people who have the factor V Leiden mutation but who have not experienced abnormal blood clots.

### However, your doctor might suggest that you take extra precautions to prevent blood clots if you have the factor V Leiden mutation and are going to have surgery. These precautions might include:

### A short course of blood thinners

### Leg wraps that inflate and deflate to keep blood moving in your legs

### Compression stockings

### Going for walks soon after surgery

## Lifestyle and home remedies

### Some precautions to help reduce your risk of blood clots include:

### Keep your legs moving. When your legs remain still for hours, your calf muscles don't contract, which normally helps blood circulate. If you're on a long plane trip, raise your toes up and down and rotate your ankles every hour or so. Drink extra water to prevent dehydration, and avoid alcohol. On a car trip, take periodic breaks and walk around.

### Consider compression stockings. These types of socks, which usually come up to the knees, help improve blood circulation in your legs. Ask your doctor if they might be a good option for your situation.

### Be cautious with estrogen. Oral contraceptives or estrogen replacement therapy can increase the risk of blood clots on their own, so be sure to discuss the risks and the benefits of estrogen-containing medications with your doctor if you have factor V Leiden.

### Prevent excessive bleeding

### If your factor V Leiden requires you to take anticoagulant medication, here are some steps that might help you prevent injury and avoid excessive bleeding:

### Avoid playing contact sports or engaging in other activities that could result in physical injury. Regular non contact exercise, such as walking or swimming, is still recommended for good health.

### Use a soft toothbrush and waxed floss.

### Avoid shaving cuts by using an electric razor.

### Be cautious with household tasks involving knives, scissors and other sharp tools.

### 

### When to see a doctor

Seek medical attention immediately if you have signs or symptoms of either a DVT or a pulmonary embolism.

**COMPLICATION**

Factor V Leiden can cause blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism). These blood clots can be life-threatening.

**PROGNOSIS**

A proportion of the population with factor V Leiden will suffer from venous thrombosis. Thromboembolism, including pulmonary embolism, carries significant morbidity and mortality. However, despite the increase in the risk of VTE, there is no evidence that heterozygosity to factor V Leiden increases overall mortality.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for deep vein thrombosis (DVT) includes the following:

**Inherited Thrombophilia**

* Prothrombin G20210A mutation
* Protein S deficiency
* Protein C deficiency
* Antithrombin (AT) deficiency

**Others**

* Malignancy
* Trauma/surgery
* Pregnancy or use of oral contraceptives
* Immobilization/obesity
* Nephrotic syndrome
* Antiphospholipid syndrome
* Paroxysmal nocturnal hemoglobinuria
* Myeloproliferative disorders
* Heart failure
* Severe liver disease.cirrhosis
* Medications like tamoxifen, thalidomide, or lenalidomide

**EPIDEMIOLOGY**

Heterozygosity of the factor V Leiden mutation is the most common inherited thrombophilia in the unselected White population (prevalence, approximately 1% to 5%) and is considered the most common inherited thrombophilia in individuals with venous thromboembolism (prevalence of roughly 10% to 20%).[[2]](https://www.ncbi.nlm.nih.gov/books/NBK534802/#) Heterozygosity of this genetic mutation increases the lifetime risk of thrombosis by about 7-fold, while homozygosity (which is rare) increases the risk by approximately 20-fold. Despite the increase in the risk of VTE, there is no clinical evidence that heterozygosity of factor V Leiden increases overall mortality.

REFERENCES

[Factor V Leiden Mutation - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK534802/#article-21577.s10)

[Factor V Leiden - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/factor-v-leiden/diagnosis-treatment/drc-20372428)

[Factor V Leiden - Symptoms and causes - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/factor-v-leiden/symptoms-causes/syc-20372423)

### 

### 

### Thrombocytopenia

**DEFINITION AND DESCRIPTION**

Thrombocytopenia (pronounced “THROM-bo-sigh-toe-PEE-ne-ah”) occurs when your bone marrow doesn’t make enough platelets. Platelets are blood cells that form blood clots to help stop bleeding. If you have thrombocytopenia, you may bleed a lot, and the bleeding may be hard to stop.

Thrombocytopenia often affects people with certain medical conditions, like autoimmune disease or who take certain medications. Healthcare providers typically treat thrombocytopenia by treating the underlying condition and/or changing the medication that caused the issue.

#### How common is this condition?

People may have thrombocytopenia and not realize it because their symptoms are so mild. That’s why healthcare providers aren’t sure exactly how many people have this condition. They do know a related condition, immune thrombocytopenia, affects 3 to 4 in 100,000 children and adults. About 5% of pregnant women develop mild thrombocytopenia just before giving birth.

#### Complications of thrombocytopenia

People with severe thrombocytopenia may have an increased risk of developing the following conditions:

* Severe internal bleeding: Thrombocytopenia may cause gastrointestinal bleeding or bleeding in your brain. Bleeding into your brain is a life-threatening issue.
* Heart attack: Thrombocytopenia may decrease the amount of blood flow to your heart.

What are normal platelet levels?

A normal platelet count or level in adults ranges from 150,000 to 450,000 platelets per microliter of blood. Thrombocytopenia levels are:

* Mild thrombocytopenia: Platelet levels between 101,000 and 140,000 per microliter of blood.
* Moderate thrombocytopenia: Platelet levels between 51,000 and 100,000 per microliter of blood.
* Severe thrombocytopenia: Platelet levels between 51,000 and 21,000 microliters of blood.

## Symptoms and Causes

Some people with mild cases of thrombocytopenia don’t have symptoms. When they do, one of the first symptoms is a cut or nosebleed that won’t stop bleeding. Other symptoms include:

* Bleeding gums: You may notice blood on your toothbrush and your gums may appear swollen.
* Blood in poop (stool): Your poop may appear very dark.
* Blood in urine (pee): If toilet water is pale pink after you pee, you may have blood in your urine.
* Blood in vomit: Hematemesis, or blood in vomit, is a sign of bleeding in your upper gastrointestinal tract.
* Heavy menstrual periods: If your periods last longer than seven days or you’re bleeding more than usual, you may have menorrhagia.
* Petechiae: This symptom appears as tiny red or purple dots on your lower legs that resemble a rash.
* Purpura: You may have red, purple or brown spots on your skin. This happens when small blood vessels under your skin leak blood.
* Bruises: Bruises happen when blood pools under your skin. You may notice you’re developing bruises more easily than usual.
* Rectal bleeding: You may notice blood in the toilet water or after you wipe.

### Causes of thrombocytopenia

Thrombocytopenia causes fall into one of three categories:

* Your bone marrow doesn’t make enough platelets. This may happen if you have blood cancers like leukemia or lymphoma.
* Your bone marrow makes enough platelets, but your platelet supply runs low because you have conditions that use up your platelet supply or destroy your platelets.
* Your spleen traps platelets so they can’t circulate through your bloodstream. Normally, your spleen stores about one-third of your platelet supply.

Specific factors affecting platelet supply include:

* Autoimmune diseases: Autoimmune diseases, like immune thrombocytopenia (ITP), lupus and rheumatoid arthritis, that attack your immune system may destroy platelets.
* Blood cancers: Leukemia and lymphoma may damage your bone marrow and affect its ability to make enough blood cells, including platelets.
* Cancer treatments: Treatments — including chemotherapy and radiation therapy — sometimes destroy stem cells that would have become platelets.
* Thrombotic thrombocytopenic purpura (TPP): This blood disorder causes blood clots in small blood vessels throughout your body. Platelets make blood clots. Your platelet supply may run low if you have TPP or a similar condition, disseminated intravascular coagulation, which uses up platelets.
* Infections: Bacterial and viral infections may lower your platelet levels.
* Alcohol use disorder: Alcohol slows platelet production. Drinking a lot of alcohol may cause your platelet level to drop.
* Toxic chemicals: Exposure to toxic chemicals, including arsenic, benzene and pesticides, may affect your platelet level.
* Medications: Antibiotics that treat bacterial infections, medication for seizures and heart conditions, and the blood thinner heparin may affect platelet levels.

## Diagnosis and Tests

Healthcare providers will do a physical examination. They’ll check for bruises, rashes and other thrombocytopenia symptoms. They’ll ask about your medical history, including any medications you take. They may do tests including:

* Complete blood count (CBC): Providers will check your platelet levels and your white and red blood cell levels.
* Peripheral blood smear: Providers examine your platelets under a microscope.
* Blood clot test: A blood clot test measures the time it takes blood to clot. These tests include partial thromboplastin time (PTT) and prothrombin time (PT) tests.
* Bone marrow biopsy: If blood tests show a low platelet count, your healthcare provider may do a bone marrow biopsy.

## Management and Treatment

You might not need treatment if a low platelet count isn’t causing significant issues. Often, healthcare providers can improve platelet counts by treating the underlying cause. This approach may involve changing your medications. Other treatments include:

* Steroids: These medications may boost your platelet production.
* Blood transfusion: If your platelet level is very low, your healthcare provider may use blood transfusions to temporarily increase your platelet levels. Transfusions may boost levels for about three days.
* Splenectomy: This is surgery to remove your spleen. Your surgeon may do this if tests show your spleen is trapping large numbers of platelets. People who have splenectomies have an increased risk of developing infections. They may receive vaccinations to prevent infections.

## Outlook / Prognosis

Many things can cause your platelet levels to drop so you develop thrombocytopenia. For example, you may have an autoimmune disease that affects your platelet levels. You may have low platelet levels because you drink lots of alcohol or are exposed to certain toxic chemicals.

Bottom line — once your healthcare provider finds out why your platelet levels are low, they’ll take steps to help you. If you have thrombocytopenia, ask your healthcare provider what caused the issue and what treatment or lifestyle changes they recommend.

If your provider recommends treatment, you may need ongoing treatment to maintain a normal platelet level. Your provider will monitor your overall health and platelet levels.

## Prevention of thrombocytopenia

The most important thing is to understand if you have medical conditions or take medication that increases your risk of developing thrombocytopenia. If you do, ask your healthcare provider if there are medications or activities you should avoid.

## Living With

If you have thrombocytopenia, here are some suggested ways to take care of yourself:

* Make healthy lifestyle changes: If you smoke, quit. Smoking increases your risk of blood clots. If you drink alcohol, do so in moderation. Heavy alcohol use may affect platelet levels. Practice good dental hygiene to avoid dental treatments that may cause bleeding.
* Take care with over-the-counter (OTC) medication: Some OTC medications contain ibuprofen or aspirin that may make your blood too thin. Talk to your provider before using supplements and herbal remedies.
* Avoid activities that may cause bruising and bleeding: Most contact sports, like football, soccer or basketball, increase the chance you’ll have an injury that involves bleeding. Ask your healthcare provider about activities you can do without increasing your risk of injury.
* Travel safe: Wear your seatbelt while driving or riding in a vehicle.
* Tell your healthcare providers about your medications: You may receive medication to thin your blood. If you have surgery or dental procedures, tell your providers about your medications before your surgery or procedure.

### When should I seek care?

Thrombocytopenia symptoms can develop very quickly or over time. It may also cause bleeding in many parts of your body. Seek medical care if:

* You notice changes in your body that could be thrombocytopenia symptoms, such as new bruises and unusual bleeding.
* You have a fever or other signs of infection. If you had a splenectomy, you’re at increased risk of infection.

**DIFFERENTIAL DIAGNOSIS**

Psuedothrombocytopenia: Invitro platelet clumping results from ethylenediaminetetracetic acid (EDTA) dependent agglutinins, inadequately anticoagulated specimen, glycoprotein IIb/IIIa inhibitors. Giant platelets are counted as white blood cells rather than platelets by an automated counter.

**EPIDEMIOLOGY**

Normal platelet count range varies by different ages, sexes, and ethnicity. Women, young individuals, and non-Hispanic blacks have slightly higher platelet counts.

REFERENCES

[Thrombocytopenia - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK542208/#article-30093.s12)

[Thrombocytopenia: Symptoms, Stages & Treatment](https://my.clevelandclinic.org/health/diseases/14430-thrombocytopenia)

## Part 3: Patient Education – Common Questions and Answers

Patients diagnosed with blood disorders or cancers often seek clarity on their condition, treatment, and lifestyle impacts. Below are common questions and answers tailored to each condition, addressing typical patient concerns.

### For Anemia

* **What is anemia?**
  + Anemia occurs when the body lacks sufficient healthy red blood cells or hemoglobin, reducing oxygen delivery to tissues.
* **What causes anemia?**
  + Causes include iron or vitamin deficiencies, chronic diseases (e.g., kidney disease), bone marrow disorders, or inherited conditions like sickle cell disease.
* **What are the symptoms of anemia?**
  + Symptoms include fatigue, shortness of breath, pale skin, dizziness, and chest pain.
* **How is anemia diagnosed?**
  + A blood test measuring hemoglobin levels, often followed by tests to pinpoint the cause.
* **How is anemia treated?**
  + Treatment may involve iron or vitamin supplements, dietary changes, or managing underlying conditions.
* **Can anemia be prevented?**
  + A balanced diet rich in iron, folate, and vitamin B-12 can prevent some types; managing chronic conditions also helps.

### For Sickle Cell Disease

* **What is sickle cell disease?**
  + It’s an inherited disorder where red blood cells become sickle-shaped, causing pain and organ damage.
* **How is sickle cell disease diagnosed?**
  + Newborn screening or genetic testing confirms the condition, often before symptoms appear.
* **What are the treatment options?**
  + Pain management, hydroxyurea, blood transfusions, and, in severe cases, bone marrow transplantation.
* **Can sickle cell disease be cured?**
  + Bone marrow transplantation offers a potential cure but is high-risk and not suitable for all patients.

### For Hemophilia

* **What is hemophilia?**
  + A genetic disorder where blood fails to clot properly due to missing or defective clotting factors.
* **How is hemophilia treated?**
  + Regular clotting factor infusions, avoiding blood-thinning medications, and physical therapy for joint health.
* **Is hemophilia curable?**
  + No, but effective management allows patients to lead normal lives.

### For Von Willebrand Disease

* **What is von Willebrand disease?**
  + The most common inherited bleeding disorder, caused by deficient or defective von Willebrand factor.
* **How is it treated?**
  + Mild cases may need only lifestyle adjustments; severe cases use desmopressin or factor concentrates.
* **Can I live normally with this condition?**
  + Yes, with proper management, most patients lead active lives.

### For Thrombophilia

* **What is thrombophilia?**
  + A condition increasing the risk of abnormal blood clots, like DVT or PE.
* **How is it managed?**
  + Anticoagulants prevent or treat clots; long-term therapy may be needed for recurrent risks.
* **Can clots be prevented?**
  + Staying active, avoiding prolonged immobility, and following medical advice reduce risks.

### For Leukemia

* **What is leukemia?**
  + A cancer of the blood and bone marrow with excessive abnormal white blood cells.
* **What are the symptoms of leukemia?**
  + Fatigue, frequent infections, easy bruising, bone pain, and swollen lymph nodes.
* **How is leukemia treated?**
  + Treatments include chemotherapy, targeted therapies, immunotherapy, or stem cell transplantation, based on type and stage.

### For Lymphoma

* **What is lymphoma?**
  + A cancer of the lymphatic system where abnormal lymphocytes grow uncontrollably.
* **What are the symptoms of lymphoma?**
  + Swollen lymph nodes, fever, night sweats, weight loss, and fatigue.
* **How is lymphoma treated?**
  + Chemotherapy, immunotherapy, radiation, or stem cell transplantation, depending on the type and stage.

### For Multiple Myeloma

* **What is multiple myeloma?**
  + A cancer of plasma cells causing bone damage, kidney issues, and immune suppression.
* **What are the symptoms of multiple myeloma?**
  + Bone pain, fatigue, frequent infections, and kidney problems.
* **How is multiple myeloma treated?**
  + Chemotherapy, immunomodulators, proteasome inhibitors, stem cell transplantation, and bone-strengthening drugs.

## Recent Advancements

Research in hematology/oncology is advancing rapidly. For example, targeted therapies like tyrosine kinase inhibitors have transformed CML into a manageable chronic condition. Immunotherapies, such as CAR-T cell therapy, show promise for lymphomas and leukemias. Gene therapies are being explored for hemophilia and sickle cell disease, potentially offering cures. Clinical trials provide access to cutting-edge treatments (10).

## Conclusion

Hematology/Oncology encompasses a broad spectrum of conditions, from manageable disorders like anemia to complex cancers like multiple myeloma. Advances in diagnostics and treatments have improved outcomes, though challenges remain for incurable diseases. Patient education is crucial, empowering individuals to understand their condition, explore treatment options, and engage in shared decision-making with their healthcare team. By addressing common questions, this report aims to support patients in navigating their journey with confidence.

## References

(1) American Society of Hematology - Blood Disorders Overview. https://www.hematology.org/education/patients/blood-disorders  
(2) American Society of Hematology - Anemia Patient Guide. https://www.hematology.org/education/patients/anemia  
(3) American Society of Hematology - Sickle Cell Disease Guide. https://www.hematology.org/education/patients/anemia/sickle-cell-disease  
(4) American Society of Hematology - Bleeding Disorders Guide. https://www.hematology.org/education/patients/bleeding-disorders  
(5) Cleveland Clinic - Blood Disorders. https://my.clevelandclinic.org/health/diseases/21545-blood-disorders  
(6) American Society of Hematology - Leukemia Patient Guide. https://www.hematology.org/education/patients/blood-cancers/leukemia  
(7) American Cancer Society - Acute Lymphocytic Leukemia Overview. https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/what-is-all.html  
(8) American Society of Hematology - Lymphoma Patient Guide. https://www.hematology.org/education/patients/blood-cancers/lymphoma  
(9) American Society of Hematology - Myeloma Patient Guide. https://www.hematology.org/education/patients/blood-cancers/myeloma  
(10) American Society of Hematology - Clinical Trials. https://www.hematology.org/education/patients/clinical-trials  
(11) Mayo Clinic - Hematology Conditions Treated. https://www.mayoclinic.org/departments-centers/hematology/sections/conditions-treated/orc-20201285  
(12) Cancer Center - Blood Cancers Information. https://www.cancercenter.com/blood-cancers