

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Related Conditions

No. 40 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- MGUS is a condition in which abnormal plasma cells produce too much M protein in the blood.
- It is often found during routine blood tests. It is not a cancer.
- When MGUS turns into myeloma, the excess amount of M protein can lead to damage of the organs and decrease the body's ability to fight infection.
- Individuals with MGUS usually do not have any symptoms but are monitored carefully.
- About 1 percent of individuals diagnosed with MGUS will develop blood cancer such as multiple myeloma (cancer of the plasma cells) per year.
- Currently there is no treatment indicated for MGUS.
- Related conditions are monoclonal gammopathy of neurological significance (MGNS), monoclonal gammopathy of renal significance (MGRS) and smoldering multiple myeloma (SMM).

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic (showing no symptoms) condition in which an abnormal monoclonal protein (M protein) is present in the blood. Monoclonal means there is only one type of this abnormal protein derived from a single cell.

It is not a blood cancer, and most people with MGUS don't develop blood cancer. However, it is important the condition be monitored, since increasing levels of this protein may indicate a risk of progressing to smoldering multiple myeloma (SMM), myeloma, lymphoma, light chain amyloidosis or Waldenström macroglobulinemia. See *Health Terms* on page 5 to learn more about these diseases or visit www.LLS.org/booklets to view, print or order free LLS publications.

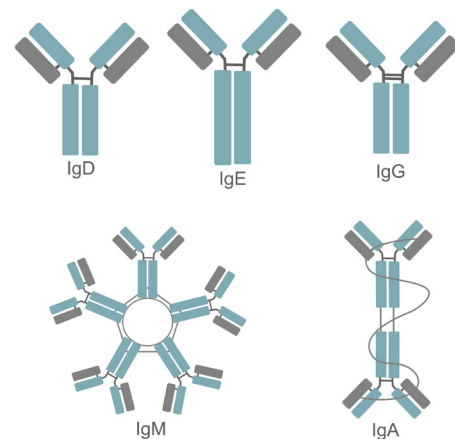
Monoclonal Gammopathy of Undetermined Significance

There are three main types of cells in the blood: red blood cells, which carry oxygen; platelets, which help the blood to clot; and white blood cells, which help fight infection. The white blood cells include lymphocytes, a key part of the immune system. The three major types of lymphocytes are:

- B lymphocytes (B cells)
- T lymphocytes (T cells)
- Natural killer cells (NK cells)

Plasma cells are derived from B lymphocytes. In the majority of cases, MGUS starts in the plasma cells.

Normal plasma cells produce immunoglobulins (also known as antibodies); they are protein molecules that help fight infection. Each type of plasma cell produces a single type of immunoglobulin which is made up of two heavy chains (either IgM, IgG, IgA, IgD or IgE) and two light chains (kappa or lambda).



When a particular plasma cell is copied many times, an excess amount of the type of immunoglobulin called M protein builds up in blood and urine. When MGUS progresses to multiple myeloma, and related conditions such as amyloidosis, it can lead to damage to the kidneys, heart and nerves, and reduce the body's ability to fight infection.

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There are three main subtypes of MGUS:

- **Non-IgM MGUS**—Also called plasma cell MGUS, this is the most common subtype. It involves IgG, IgA, IgD or IgE immunoglobulins. It may progress to myeloma or related plasma cell disorders. The type of immunoglobulin that most commonly progresses to myeloma is IgG.
- **IgM MGUS**—This subtype produces immunoglobulin M (IgM) and may progress to Waldenström macroglobulinemia, lymphoma, light chain amyloidosis, IgM myeloma or other related disorders.
- **Light chain MGUS**—This subtype is characterized by M protein without the heavy chain component. It may progress to light chain smoldering multiple myeloma, light chain multiple myeloma or light chain amyloidosis.

Symptoms

MGUS does not typically cause any symptoms, though some studies have shown association with peripheral neuropathy (numbness or tingling in the hands or feet). There is no evidence of bone damage, kidney damage, anemia (low levels of red blood cells), or elevated calcium levels. However, patients should watch for the symptoms listed below and report any to their doctor.

Bone or nerve pain	Easy bruising or bleeding
Fatigue or weakness	Fevers
Headache or dizziness	Night sweats
Numbness or tingling in fingers or toes	Swollen lymph nodes or spleen
Unexplained weight loss	Vision or hearing changes

Diagnosis

MGUS is usually detected following a routine blood test. An initial follow-up appointment within 3 to 6 months after the diagnosis is common for most people with MGUS. An assessment of risk factors can be used to help determine the risk of progression to myeloma and the frequency of monitoring. If the risk is low, less frequent follow-up will be recommended.

Diagnosis may involve blood and urine tests, imaging tests and a bone marrow biopsy. The doctor will be looking for a blood M protein level of less than 3 grams per deciliter and a bone marrow plasma cell level of less than 10 percent. The doctor will also look for evidence of other B-cell disorders.

Criteria for Diagnosing MGUS

- M protein less than 3 grams per deciliter in the blood
- Bone marrow plasma cells less than 10 percent
- No CRAB criteria:
 - C—Calcium elevation (high levels of calcium in the blood; also known as “hypercalcemia”)
 - R—Renal insufficiency (poor function of the kidneys that may be due to a reduction in blood flow to the kidneys)
 - A—Anemia (low red blood cell counts)
 - B—Bone abnormalities (lesions)
- No SLiM criteria:
 - S—60% or greater bone marrow plasma cells
 - Li—Serum free light chain ratio (involved/uninvolved)>100, with involved serum free light chain>100 mg/dl
 - M—>1 focal bone lesion on MRI

Specialized Laboratory Tests Used in MGUS

- **Electrophoresis**—Electrophoresis is a laboratory technique used to separate DNA, RNA or protein molecules based on their size and electrical charge. If present, the excessive production of monoclonal immunoglobulin (M protein) may appear on test results as a spike on a graph. ‘M spike’ is the name for this characteristic rise.
 - **Immunofixation electrophoresis (IFE)**—This test identifies the type and amount of M protein (IgG, IgA, IgD, IgE or IgM) in a blood sample. It uses both electrophoresis and an additional process called precipitation to examine the proteins.
 - **Serum protein electrophoresis (SPEP)**—This test measures the types of specific proteins in the fluid part of a blood sample.
 - **Urine protein electrophoresis (UPEP)**—This test measures how much of certain proteins are in the urine. A clean-catch urine sample is needed.
- **MASS-FIX (MALDI-TOF MS)**—MASS-FIX is a new approach that uses matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) to detect and quantify M protein. It is more sensitive than immunofixation. However, it is currently offered only at select laboratories.

MGUS Monitoring and Management Guidelines

MGUS is a rare condition. It's best to seek care at a center with doctors called hematologist-oncologists, who are experienced in the care of patients who have MGUS or related conditions. A hematologist is a doctor who has special training in disorders of the blood; an oncologist is a doctor who has special training in cancer. Doctors with training in both hematology and oncology have particular expertise in treating blood cancers.

The International Myeloma Working Group (IMWG), a collaborative research organization, recommends doctors complete a full physical examination of the patient, plus blood work, with an emphasis on symptoms that may suggest multiple myeloma. See below for MGUS information about risk factors and risk categories according to the IMWG. For more information about the IMWG, see *Other Resources* on page 7.

Risk factors for progression to more advanced disease:

- M protein level more than 1.5g/dL
- M protein type is IgA or IgM
- Abnormal serum free light chain ratio of kappa to lambda

Risk categories:

- Low: None of the three risk factors are present
- Low intermediate: One risk factor is present
- High intermediate: Two risk factors are present
- High risk: All three risk factors are present

Low Risk: If blood work shows the serum M protein is low (of the IgG type) and the free light chain ratio is normal, patients are categorized as low risk. In this scenario, patients are followed with a serum protein electrophoresis test at six months and, if stable, followed every two to three years until symptoms of multiple myeloma or a related disease appear.

Intermediate or High Risk: If a patient with MGUS has a high M protein level of IgA or IgM type and an abnormal free light chain ratio, a bone marrow aspiration and biopsy should be considered to rule out multiple myeloma or a related disease. These patients are monitored with a serum protein electrophoresis test again in six months and then annually until symptoms of multiple myeloma or a related disease appear.

Most patients with a diagnosis of MGUS will never

progress to aggressive disease. However, it is important for both doctors and patients to keep in mind the psychological burden (anxiety, worry) of ongoing monitoring.

Visit www.LLS.org/booklets to view the LLS publication *Watch and Wait*. This publication has information about watch and wait for blood cancers but pertains to MGUS watch and wait patients as well.

Cause, Risk Factors and Incidence

The cause of MGUS is unknown. In most cases of MGUS an abnormal plasma cell produces an abundance of M protein.

Myeloma is a cancer of the plasma cells. Almost all myeloma patients have MGUS before the condition progresses to myeloma, but only 20 percent of people diagnosed with MGUS eventually develop myeloma. The associated risk of MGUS progressing to myeloma is approximately 1 percent per year.

As a diagnosis of myeloma is almost always preceded by MGUS, the same theories that apply to the development of myeloma may apply to MGUS. Visit www.LLS.org/booklets to read more in the LLS booklet *Myeloma*.

MGUS occurs in approximately three percent of adults aged 50 or older and five percent of adults over the age of 70. In addition to older age, risk factors include male sex, exposure to pesticides, and family history of MGUS or myeloma. Infection, autoimmune diseases, genetics, smoking and the environment may play a role.

The prevalence of MGUS is higher in African Americans. In addition, a recent observational study reported an increased risk of MGUS among rescue and recovery workers at the World Trade Center disaster site.

There is no way to prevent MGUS.

Future Directions

Research studies are being done to determine the risk of progression (of MGUS to advanced disease) more clearly and to see if the high-risk group of patients might benefit from treatment. Currently there is no treatment indicated for MGUS outside of a clinical trial. Visit www.LLS.org/clinicaltrials for more information about clinical trials and the LLS Clinical Trial Support Center.

Recent advances in molecular and genomic techniques are improving our understanding of MGUS and its related conditions.

Related Conditions

Monoclonal Gammopathy of Neurological Significance (MGNS)

Some patients with MGUS experience peripheral neuropathy (weakness, tingling, numbness or pain in the hands and feet) due to damage to the nerves. It is essential for a doctor, preferably a neurologist (a doctor who has specialized training in disorders that affect the brain, spinal cord and nerves), to rule out other possible causes of the peripheral neuropathy. There is limited data on treatment for MGNS.

Monoclonal Gammopathy of Renal Significance (MGRS)

Monoclonal gammopathy of renal significance is a group of disorders in which the monoclonal immunoglobulin (M protein) produced by plasma cells or B cells cause renal (kidney) damage. Though it is not a cancer, its effects on the kidneys may be serious.

Lesions (damaged tissue) are primarily caused by the presence of the M protein (either the entire immunoglobulin or the light chain; rarely the heavy chain) in the kidney. Parts of the kidney that may be involved are the:

- Glomeruli (network of blood vessels that act as a filter)
- Tubules (tiny ducts that help filter blood)
- Blood vessels (veins, arteries)
- Interstitium (fluid-filled space)

The hematologist-oncologist and a nephrologist (a doctor who has special training in disorders of the kidneys) often work together to help patients with MGRS.

A kidney biopsy is recommended in most cases to diagnosis MGRS. There may also be blood, urine, bone marrow and imaging tests.

The aim of treatment for MGRS is to preserve or improve kidney function by eliminating the abnormal cells. Treatment may include drugs such as those used in chemotherapy or immunotherapy, and/or medications to reduce inflammation. In some cases, treatment can include a stem cell transplant, dialysis or a kidney transplant.

Smoldering Multiple Myeloma (SMM)

Smoldering multiple myeloma is an asymptomatic disorder. It is diagnosed when a person's blood or urine contains a certain amount of M protein, but the person

has no symptoms of myeloma. However, it carries a risk of progression to myeloma of approximately 10 percent per year for the first five years; 3 percent per year for the next five years; and 1 to 2 percent per year for the following 10 years.

The diagnostic process for SMM includes blood and urine tests, imaging tests, and a baseline bone marrow biopsy.

Criteria for Diagnosing Smoldering Multiple Myeloma

- M protein in the serum of greater than or equal to 3 grams per deciliter
- Or urinary M protein greater than 500 milligrams per 24 hours and/or
- Bone marrow plasma cells greater than or equal to 10 percent
- No CRAB criteria: C—Calcium elevation; R—Renal insufficiency; A—Anemia; B—Bone abnormalities
- No SLiM criteria: S—60% or greater bone marrow plasma cells; Li—Serum free light chain ratio (involved/uninvolved)>100, with involved serum free light chain>100 mg/dl; M—>1 focal bone lesion on MRI

Testing should be done 2 to 3 months after the initial diagnosis of SMM. If the results are stable, the patient should be followed every 4 to 6 months for 1 year and, if stable, every 6 to 12 months.

Risk Stratification

Individuals diagnosed with SMM are classified into risk groups. The commonly used Mayo 2018/IMWG risk stratification system is based on three risk factors:

- M protein greater than 2 grams per deciliter
- Bone marrow plasma cells greater than 20 percent
- Free light chain ratio greater than 20

Low Risk: No factors are present.

Intermediate Risk: One factor is present.

High Risk: Two or three factors are present.

Another risk factor to be considered is the presence of cytogenetic abnormalities such as broken, missing, rearranged or extra chromosomes.

Low risk and intermediate risk patients are closely monitored and/or enrolled in a clinical trial. Patients with 2 or 3 risk factors are considered high risk. For patients that are high risk, options include active surveillance (watch and wait), early treatment, and clinical trials.

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In recently published clinical practice guidelines from the National Comprehensive Cancer Network (NCCN), an alliance of leading cancer centers, some individuals with high risk SMM may fall into a select group for which treatment with lenalidomide (Revlimid®) may be considered.

Visit www.LLS.org/clinicaltrials for more information about clinical trials and the Clinical Trial Support Center.

Health Terms

Amyloidosis—A group of diseases in which abnormal proteins build up in certain organs or throughout the body. Instead of forming immunoglobulins, the abnormal proteins misfold and form amyloid. Primary or light chain (AL) amyloidosis is the most common type.

Antibody—A protein made by plasma cells (a type of white blood cell) in response to an antigen. An antibody is a type of immunoglobulin. It is a Y-shaped structure consisting of four polypeptides: two heavy chains (containing 440 amino acids) and two light chains (containing 220 amino acids).

Antigen—A substance that causes the body to make a specific immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, etc.

Bone marrow biopsy—A procedure in which a sample of bone containing bone marrow is removed, usually from the hip bone, for examination by a pathologist (a doctor who has special training in identifying diseases by studying cells and tissues under a microscope).

Heavy chain—An antibody with only two heavy chains and lacking the two light chains normally found in antibodies.

Immunoglobulin—A protein made by B cells and plasma cells (types of white blood cells) that helps the body fight infection.

Light chain—Light chains are pieces of an antibody made by the plasma cells in the bone marrow. There are two types: kappa and lambda.

Lymphoma—The term for a group of blood cancers that originate in the lymphatic system, part of the body's immune system. The two major types are Hodgkin lymphoma and non-Hodgkin lymphoma. Visit www.LLS.org/booklets to view lymphoma-related publications.

M protein—M protein is the simplified term for a type of protein made in large amounts by abnormal, cancerous or precancerous plasma cells and secreted into the blood.

M protein is also called monoclonal protein, monoclonal immunoglobulin, and paraprotein.

M spike—The M protein shows up as a sharp spike on the protein electrophoresis test.

Myeloma—A cancer that arises in plasma cells, a type of white blood cell. The plasma cells produce abnormal proteins which may accumulate in tissues and damage the kidneys, heart, or other organs, and affect immune system function. Visit www.LLS.org/booklets to view myeloma-related publications.

Serum—Serum is the colorless, liquid part of the blood in which cells are suspended.

Smoldering multiple myeloma—A very slow-growing type of myeloma in which abnormal plasma cells make too much of a single type of monoclonal protein. The protein builds up in the blood or is passed in the urine. Patients don't usually have symptoms but need to be monitored closely for signs of progression to fully developed myeloma.

Waldenström macroglobulinemia—A slow-growing type of non-Hodgkin lymphoma marked by abnormal levels of IgM antibodies in the blood and an enlarged liver, spleen or lymph nodes. Also called lymphoplasmacytic lymphoma. Visit www.LLS.org/booklets to view the free LLS publication *Waldenström Macroglobulinemia*.

Feedback. To make suggestions about the content of this booklet, visit www.LLS.org/PublicationFeedback.

Acknowledgement

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We're Here to Help

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

For Help and Information

Consult with an Information Specialist. Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our

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Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Nutrition Consultations. Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit www.LLS.org/nutrition for more information.

Free Information Booklets. LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more

information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

3D Models. LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit www.LLS.org/3D for more.

Free Mobile Apps.

- LLS Coloring For Kids™ — Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ — Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Connecting with Patients, Caregivers and Community Resources

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit www.LLS.org/chat for more information.

Local Programs. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/LocalPrograms

Advocacy and Public Policy. Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care

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more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit www.LLS.org/advocacy for more information.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Additional Help

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please:

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please:

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

Help with Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter “depression” in the search box

Other Resources

International Myeloma Foundation (IMF)
800-452-2873
<https://www.myeloma.org/>

The mission of the IMF is to improve the quality of life of myeloma patients and their families while working toward prevention and a cure through four founding principles: research, education, support, and advocacy. The IMF supports the work of the International Myeloma Working Group (IMWG) which conducts research.

Multiple Myeloma Research Foundation (MMRF)
203-229-0464
<https://themmrf.org/>

The mission of the MMRF is to pursue innovative means that accelerate the development of next-generation multiple myeloma treatments to extend the lives of patients and lead to a cure.

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