MDA Muscular Dystrophy Association

Myasthenia Gravis (MG)

Myasthenia gravis (MG) is a chronic autoimmune disease — a disease that occurs when the immune system mistakenly attacks the body's own tissues.

In MG, the immune system attacks and interrupts the connection between nerve and muscle, called the **neuromuscular junction (NMJ)**. This causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body.

In most cases of MG, the immune system targets the **acetylcholine receptor (AChR)** — a protein on muscle cells that is required for muscle contraction.

About 85% of people with MG are **AChR antibody-positive**. This means they have antibodies against AChR in their blood. The antibodies target and destroy many of the acetylcholine receptors on muscle cells. Consequently, the muscle's response to repeated nerve signals declines with time, and the muscles become weak and tired.

About 15% of individuals with MG are **seronegative for antibodies** to AChR, meaning the antibodies aren't detectable in their blood (serum). It's been discovered that a large fraction of these individuals are **MuSK antibody-positive**. This means they have antibodies to **muscle-specific kinase (MuSK)**, a protein that helps organize acetylcholine receptors on the muscle cell surface.

There's also evidence that an immune system gland called the **thymus** plays a role in MG. About 10%-15% of people with MG have a thymic tumor, called a **thymoma**, and another 65% have overactive thymic cells, a condition called **thymic hyperplasia**. When the thymus doesn't work properly, the immune system may lose some of its ability to distinguish self from non-self, making it more likely to attack the body's own cells.

MG affects both men and women and occurs across **all racial and ethnic groups**. It most commonly impacts young adult women (younger than 40) and older men (older than 60), but it **can occur at any age**, including during childhood.

MG is **not inherited, and it is not contagious**. Although MG is not hereditary, genetic susceptibility appears to play a role in it. Occasionally, the disease may occur in more than one member of the same family.

MG causes **weakness** in muscles that control the eyes, face, neck, and limbs. Symptoms include partial paralysis of eye movements, double vision, and droopy eyelids, as well as weakness and **fatigue** in the neck and jaw, with problems in chewing, swallowing, and holding up the head.

MG presents in two main forms:

- **Ocular MG:** Weakness is limited to the muscles that control eyelids and eye movement (ocular muscles)
- **Generalized MG (gMG):** Weakness may affect ocular muscles and a combination of bulbar (e.g., tongue, jaw, throat), limb (e.g., arm, leg), and respiratory (e.g., breathing) muscles

More than 50% of people with MG present with ocular symptoms. Of those who have ocular symptoms, approximately half develop gMG within two years. Currently, there is no way to predict whether a person with ocular MG will develop gMG.

Muscle weakness in MG gets **worse with exertion and improves with rest**.

Approximately 10%-20% of people with MG experience at least one **myasthenic crisis**, an emergency in which the muscles that control breathing weaken to the point where the individual requires a ventilator to help them breathe. This condition may be triggered by infection, stress, surgery, or an adverse reaction to medication, and usually requires immediate medical attention.

The morbidity and mortality associated with myasthenic crisis have declined sharply due to the availability of treatments and improvements in intensive and ventilatory care.

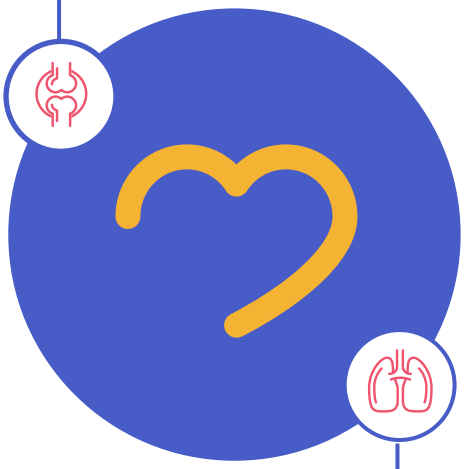
There is no known cure for MG, but there are treatments that can control symptoms and allow people with MG to have a relatively high quality of life. Most individuals with the condition have a normal life expectancy.

Most people with MG are able to manage their symptoms and lead active lives, and a few experience remission lasting many years.

What Are the Signs and Symptoms of MG?

Skeleton and muscle:

- Muscle weakness
- Partial paralysis of eye movements
- Drooping of one or both eyelids
- Blurred vision
- Double vision
- Change in facial expression
- Difficulty chewing or swallowing
- Impaired speech



Lungs

- Shortness of breath

To learn more about MG and MDA's programs, visit **MDA.org** or contact the MDA Resource Center at **833-ASK-MDA1 (275-6321)** or **ResourceCenter@mdausa.org**.

What Should I Know About MG?

1. The onset of MG may be sudden, and symptoms sometimes may not be immediately identified as being caused by MG.

2. Early in its course, MG tends to affect the muscles that control movement of the eyes and eyelids, causing ocular weakness. Consequently, a partial paralysis of eye movements, double vision, and droopy eyelids are usually among the first symptoms of MG.

3. Weakness and fatigue in the neck and jaw also can occur early in MG. This bulbar weakness — named for the nerves that originate from the bulblike part of the brainstem — can make it difficult to talk, chew, swallow, and hold up the head.

4. The degree of muscle weakness involved in MG varies greatly among individuals, ranging from a localized form limited to eye muscles (ocular MG), to a severe or generalized form (gMG) in which many muscles — sometimes including those that control breathing — are affected.

5. In gMG, weakness tends to spread sequentially from the face and neck to the upper limbs, the hands, and then the lower limbs. It may become difficult to lift the arms over the head, rise from a sitting position, walk long distances, climb stairs, or grip heavy objects. In some cases, weakness may spread to muscles in the chest that control breathing.

6. Sometimes the severe weakness of MG may cause respiratory failure, which requires immediate emergency medical care.

7. Many prescription drugs can unmask or worsen symptoms of MG. These include: muscle relaxants used during surgery, certain classes of antibiotics, cardiac antiarrhythmics, statins, local anesthetics, and magnesium salts (including milk of magnesia).

8. Overexertion, emotional stress, infections (anything from tooth abscesses to the flu), menstruation, and pregnancy also might lead to increased weakness in MG.

9. Weakness and fatigue in MG tend to fluctuate from day to day, and even during a single day. People with the disease are often strongest in the morning after a full night's sleep, and weakest in the evening.

10. Symptoms often worsen over the first few years after onset, especially without treatment.

11. Weakness serious enough to require full-time wheelchair use is not common in MG. Most people, when properly treated, find they can remain physically active.

12. Remission, a reversal of some or all symptoms, occurs in about 20% of people with MG. Usually, the remissions are temporary, with an average duration of five years, but some experience more than one remission during their lifetime. A few individuals have experienced apparently permanent remissions lasting more than 20 years.

Medical Management

Many therapeutic options are available for treating MG, each with distinct advantages and disadvantages. Use of a particular approach may depend on many factors, including but not limited to the age of the patient, the severity of the disease, antibody status, and patient preference.

- Targeted therapies (complement inhibitors, neonatal Fc receptor inhibitors, and B-cell targeted therapies)
- Symptomatic treatments (acetylcholinesterase inhibitors)
- Surgical intervention (thymectomy)
- Traditional immunotherapies (corticosteroids and non-steroidal immunosuppressive drugs)
- Rapid immunomodulating therapies (plasmapheresis and intravenous immunoglobulin)

The benefits and risks of these treatments must be weighed against each other and the needs of the patient. A doctor can help determine which treatments are appropriate.

Complement inhibitors

Complement inhibitors target a part of the immune system called the complement pathway, which helps trigger an effective immune response to potential invaders. In MG, the complement system is inappropriately recruited by antibodies to target the neuromuscular junction.

SOLIRIS® (eculizumab) is an FDA-approved intravenous infusion treatment for adults with gMG who are AChR antibody-positive. SOLIRIS is thought to work in MG by inhibiting the complement pathway to prevent destruction of the NMJ. It can improve activities of daily living and reduce disease severity.

ULTOMIRIS® (ravulizumab-cwvz) is an FDA-approved intravenous infusion for adults with AChR antibody-positive gMG. There is an initial loading dose followed by maintenance doses every eight weeks. Ultomiris is designed to target a component of the immune system (known as complement), which underlies many autoimmune disorders, including gMG.

Medical Management (continued)

ZILBRYSQ® (zilucoplan) is an FDA-approved once daily injection for adults with AChR antibody-positive gMG. It is designed to block C5, a specific complement protein involved in muscle cell damage. By reducing the cause of muscle cell damage, it can help improve the signals between nerves and muscles.

Neonatal Fc receptor inhibitors

Neonatal Fc receptor (FcRn) inhibitors work by blocking the FcRn, which normally prevents immunoglobulin G (IgG) antibodies from being broken down. Blocking it can lead to a rapid reduction in circulating disease-causing autoantibodies.

IMAAVY™ (nipocalimab-aahu) is the first FDA-approved FcRn blocker approved in AChR and MuSK antibody-positive adults and pediatric gMG patients ages 12 and older. Given as an infusion every two weeks, it decreases levels of IgG, including harmful IgG autoantibodies, by blocking the FcRn receptor.

RYSTIGGO® (rozanolixizumab-noli) is administered as an injection for subcutaneous infusion. It is the only FDA-approved treatment for adults with MG who are AChR or MuSK antibody-positive. It has been designed to block the interaction of FcRn and IgG, accelerating the catabolism of antibodies and reducing the concentration of pathogenic IgG autoantibodies.

VYVGART® (efgartigimod alfa-fcab) is the first FDA-approved treatment that uses a fragment of an IgG antibody to treat adults with all serotypes of gMG, including AChR antibody-positive, MuSK antibody-positive, LRP4 antibody-positive, and triple seronegative — who historically have faced limited or no FDA-approved treatment options specific to their subtype. It is an infusion that is given in cycles of four doses over four weeks. It binds to a protein (FcRn) and prevents the recycling of the antibodies that cause MG, which improves activities of daily living and reduces muscle weakness. A subcutaneous formulation, **VYVGART HYTRULO®** (efgartigimod alfa and hyaluronidase-qvfc), was approved by the FDA in June 2023 and is also available for adults with all serotypes of gMG.

B-cell targeted therapies

These therapies target the cells responsible for producing autoantibodies.

UPLIZNA® (inebilizumab-cdon) is the first and only CD19-targeted B-cell therapy approved for the treatment of gMG in adults who are AChR and MuSK antibody-positive. It is administered through intravenous infusion twice per year after two initial loading doses.

Rituximab, often used off-label, especially for MuSK antibody-positive gMG, is a well-established CD20-directed B-cell therapy included in many clinical guidelines for refractory cases of MG, where traditional interventions do not work well.

Acetylcholinesterase inhibitors (symptomatic treatment)

These drugs, also known as anticholinesterases, have been used to treat MG since the early 1990s and can produce relief from symptoms within minutes. Acetylcholinesterase inhibitors are considered the first drug of choice for the treatment of MG. The one most used is **Mestinon** (pyridostigmine bromide).

Medical Management (continued)

In some cases, acetylcholinesterase inhibitors can be used successfully as monotherapy to reach the patient's and the provider's treatment goals. However, most people with MG require further escalation to immunosuppressive therapy. Acetylcholinesterase inhibitors can also be used in conjunction with immunosuppressive agents to minimize the dose, and thus associated side effects, of the immunosuppressive agents

Surgical intervention

Thymectomy — surgical removal of the thymus gland — is recommended for thymic tumors and for most cases of AChR antibody-positive generalized MG. Thymectomy does not appear to play a role in MuSK antibody-positive disease. Studies have shown that thymectomy can produce long-term remission and may increase strength or reduce the need for medication in about half of patients who receive it. These improvements, however, may take several months to several years after surgery to occur. Thymectomy is not appropriate for all individuals with MG, but it can be a beneficial treatment option for carefully selected patients. Eligibility and potential benefit are influenced by factors such as age, disease severity, antibody status, and MG subtype.

Traditional immunotherapies and rapid immunomodulating therapies

Immunosuppressive drugs improve muscle strength by suppressing the production of abnormal antibodies. They include **corticosteroids** like prednisone or prednisolone (first-line immunosuppressants) or **nonsteroidal immunosuppressants**, including azathioprine, mycophenolate mofetil, and tacrolimus.

Rapid immunomodulating therapies are used primarily during a myasthenic crisis or before surgery to quickly lower antibody levels. These include **plasmapheresis** and **intravenous immunoglobulin (IVIG)**.

Plasmapheresis is a "blood filtering" procedure in which a machine is used to remove harmful antibodies in plasma and replace them with good plasma or a plasma substitute.

IVIG is a highly concentrated injection of antibodies pooled from many healthy donors that works by flooding the system with healthy antibodies to neutralize harmful ones in circulation.

MDA Glossary

Autoimmune disease
A disease characterized by an inappropriate attack of the immune system on the body's own tissues

Diplopia
Double vision

Dysarthria
Difficulty speaking or forming words

Dysphagia
Difficulty swallowing

Dyspnea
Difficulty breathing

Genetic susceptibility
An increased likelihood of developing a particular disease based on a person's genetic makeup

Myasthenic crisis
A medical emergency that occurs when the muscles that control breathing weaken to the point where individuals require a ventilator to help them breathe

Neuromuscular junction
The place where nerve cells connect with the muscles they control

Neuromuscular junction disorder
A condition that is a result of the destruction, malfunction, or absence of one or more key proteins involved in the transmission of signals between muscles and nerves

Neurotransmitter
Chemicals that neurons, or brain cells, use to communicate information

Ophthalmoparesis
Partial paralysis of eye movements

Ptosis
Drooping of the eyelids

Thymus
A gland, located in the chest behind the breast bone, that controls immune function and may be associated with MG

Images: iStock.com/adamkaz; beijingstory