REVIEW

**John A. Morren, MD**
Staff, Neuromuscular Center, and Program Director, Neuromuscular Medicine Fellowship, Neurological Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

**Yuebing Li, MD, PhD**
Neuromuscular Center, Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Myasthenia gravis: Frequently asked questions

## ABSTRACT

Myasthenia gravis is a disorder of neuromuscular junction transmission, the result of antibodies against the postsynaptic aspect of the neuromuscular junction. Its clinical hallmark is fatigable weakness of skeletal muscles, which tends to vary in location and severity among patients. It is treated with pyridostigmine, immunotherapy, and thymectomy. Treatment is often individualized according to disease severity, antibody status, comorbidities, and other factors. This review uses a question-and-answer format to provide up-to-date, high-yield, clinically relevant information on myasthenia gravis.

## KEY POINTS

- Diagnosis often starts with antibody testing, while electrodiagnostic tests are useful in selected patients.
- Pyridostigmine is often given to patients with mild symptoms, or as an ancillary therapy for patients with more severe illness.
- Corticosteroids and corticosteroid-sparing agents are given based on a variety of patient characteristics.
- Thymectomy is mostly reserved for younger patients with acetylcholine receptor antibody-positive generalized myasthenia gravis.
- Newer selective immunotherapies for myasthenia gravis are emerging.

doi:10.3949/ccjm.90a.22017

The name "myasthenia gravis" comes from the Greek for muscle weakness and the Latin word for grave or serious. A chronic autoimmune neuromuscular disorder causing skeletal muscle weakness, its primary pathophysiology involves dysfunction of the postsynaptic aspect at the neuromuscular junction, mainly a loss of acetylcholine receptor (AChR) function on the muscle membrane.

Certain skeletal muscle groups are more likely to be involved than others, but the pattern varies widely among patients and depends on the clinical course in the individual patient. Accordingly, myasthenia gravis is typically categorized as either ocular (in which weakness is limited to the extrinsic ocular muscles and levator palpebrae superioris), or generalized (in which muscles beyond those in the ocular form are involved, including those of the limbs, the bulbar and oropharyngeal region, and muscles of respiration).

The following 12 frequently asked questions and answers aim to provide up-to-date, high-yield, clinically relevant information about myasthenia gravis.

### WHICH POPULATIONS ARE AT RISK?

Family members, particularly first-degree relatives of those with myasthenia gravis, have a higher risk not only for myasthenia gravis but also for other autoimmune diseases.[1] In addition, the disease has interesting patterns of age, sex, and phenotype.

Myasthenia gravis can strike at any age, but the age of onset has a bimodal distribution, with the first peak in patients in their teens and 20s, in which girls and women outnum-

**TABLE 1**
## Key features distinguishing myasthenia gravis from other common diagnoses

| Disorder | Similarities to myasthenia gravis | Differences from myasthenia gravis |
|---|---|---|
| Lambert-Eaton myasthenic syndrome | Weakness and fatigue | Less prominent ocular or oculobulbar features<br>Areflexia or hyporeflexia<br>Autonomic features (dry mouth, erectile dysfunction)<br>Positive antibody against P/Q voltage-gated calcium channel<br>High-frequencey repetitive nerve stimulation testing shows an incremental response (ie, a progressive increase in motor amplitude) |
| Botulism | Ocular findings (diplopia and ptosis), bulbar dysfunction, generalized weakness | Acute attack, possible history of food poisoning<br>Descending paralysis<br>Dilation of the pupil (mydriasis)<br>Prominent autonomic dysfunction<br>Monophasic course<br>High-frequency repetitive nerve stimulation testing shows an incremental response |
| Amyotrophic lateral sclerosis | Bulbar dysfunction and weakness | Slow progressive course<br>No ocular findings<br>Symptoms do not fluctuate<br>Findings of upper motor neuron dysfunction (eg, hyperreflexia, spasticity)<br>Electromyography showing prominent active and chronic denervation or reinnervation, or both |
| Myopathy | Proximal limb weakness | Relative absence of ocular findings<br>Symptoms do not fluctuate<br>Creatine kinase elevation and presence of myositis-specific antibodies in cases of autoimmune or inflammatory myositis<br>Repetitive nerve stimulation testing is normal, while needle electromyography shows short-duration, low-amplitude, polyphasic motor-unit potentials, with or without abnormal spontaneous activity |
| Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy | Generalized weakness | Sensory symptoms such as pain and paresthesia<br>Symptoms do not fluctuate<br>Hyporeflexia or areflexia<br>Cerebrospinal fluid has protein elevation, no significant pleocytosis<br>Nerve conduction studies reveal findings consistent with demyelination |
| Thyroid eye disease | Diplopia | Ptosis is infrequent<br>Symptoms do not fluctuate<br>Other ocular findings such as edema, redness, conjunctival injection and exophthalmos<br>Magnetic resonance imaging showing extraocular tissue enlargement |
| Oculopharyngeal muscular dystrophy | Ptosis, diplopia, dysphagia | Slowly progressive course<br>Absence of symptomatic fluctuation<br>Relative absence of prominent limb weakness<br>Elevation of creatine kinase<br>Mutations in the PABPN1 gene; mostly autosomal dominant pattern of inheritance |

ber boys and men, and the second peak in patients in their 50s and 60s, in which men outnumber women.[2,3]

In the past, female patients outnumbered male patients overall. However, the age at onset has progressively increased, together with the proportion of men, so that the preponderance of women is becoming less.[4,5] There is a male predominance in ocular myasthenia gravis as well.[6] Boys and girls are equally affected before puberty, but more girls than boys get the disease afterward.[7]

The myasthenia gravis subtype possessing antibodies to muscle-specific tyrosine kinase (MuSK) has a marked female predominance (more than 70% in all studies reviewed), and its mean age of onset is 36 to 38 years.[2,8]

African Americans may have slightly higher rates of myasthenia gravis incidence and prevalence, and more severe disease.[9,10] In the United States, 28% to 47% of patients with MuSK antibodies are African American.[8] In addition, MuSK antibody-positive myasthenia gravis occurs in a higher proportion of those of Asian ancestry than in those of European or African ancestry.[11]

About 13% of patients with myasthenia gravis have a comorbid autoimmune disorder.[12] Thyroid disease (Hashimoto thyroiditis, Graves disease) is the most common, followed by rheumatoid arthritis.[12,13] Up to about 10% of patients with myasthenia gravis may have associated thymoma.

Fortunately, myasthenia gravis is uncommon. In a systematic review of 55 studies, Carr et al[14] calculated that the pooled incidence was 5.3 per million person-years, and the prevalence was 77.7 per million persons—both considerably lower, for example, than those of hypothyroidism or Guillain-Barré syndrome, which are in the differential diagnosis.

Although the incidence of myasthenia gravis has changed little over time, its estimated prevalence has significantly increased since the 1950s, mostly owing to improvements in diagnosis and treatment that have reduced the mortality rate, so that more people are living with the disease.

## WHEN SHOULD A CLINICIAN THINK ABOUT THIS DIAGNOSIS?

Think about myasthenia gravis when a patient has fatigable weakness, especially weakness of ocular muscles producing variable diplopia, ptosis, and weak eye-closure. These are the core clinical features. At initial presentation, which is typically subacute, up to 85% of patients have ocular symptoms.[15]

Fatigable is key. The muscle weakness fluctuates, classically worsening with sustained or repetitive physical activity, worsening by evening or nighttime, and improving with rest. In the arms and legs, the weakness generally tends to affect proximal muscles more than distal ones. In the mouth and neck, prominent bulbar weakness, including dysarthria, nasal speech, dysphagia, poor saliva control, difficulty chewing, and neck weakness including a dropped-head phenotype may be seen in about 15% of patients at presentation.[15] Myasthenia gravis-related weakness may progress in severity over weeks or months, often with exacerbations and remissions during its course.

**Think about myasthenia gravis when a patient has fatigable weakness, especially weakness of ocular muscles producing variable diplopia, ptosis, and weak eye-closure**

Of importance, patients with myasthenia gravis typically have no sensory or pain symptoms, bowel or bladder dysfunction, or changes in mental status or cognition. In addition, deep tendon reflexes are usually intact, even if the patient has marked weakness.

**Table 1** lists common disorders in the differential diagnosis of myasthenia gravis and their distinguishing features.

## WHAT TESTS SHOULD BE ORDERED?

Antibody tests are ordered first, followed in some patients by electrodiagnostic and other tests (**Figure 1**).

### Antibody tests

First-line diagnostic tests are typically serologic.

**Anti-AChR antibody** (particularly the binding subtype) is highly specific (> 90%) and very sensitive (up to about 85%) in those with generalized myasthenia gravis.[2]

**Anti-MuSK antibodies.** In patients with myasthenia gravis who are seronegative for anti-AChR antibodies, up to 37% possess anti-MuSK antibodies.[8] However, the sensitivity of anti-AChR antibody is lower, about 50%, in those who have purely ocular myasthenia gravis. Anti-MuSK antibodies rarely occur in the group of patients with purely ocular myasthenia gravis.[15]

**Antilipoprotein-related protein 4 (LRP4) antibody** is found in 3% to 50% of the remaining patients with generalized myasthenia gravis who are seronegative to both anti-AChR and anti-MuSK antibodies.

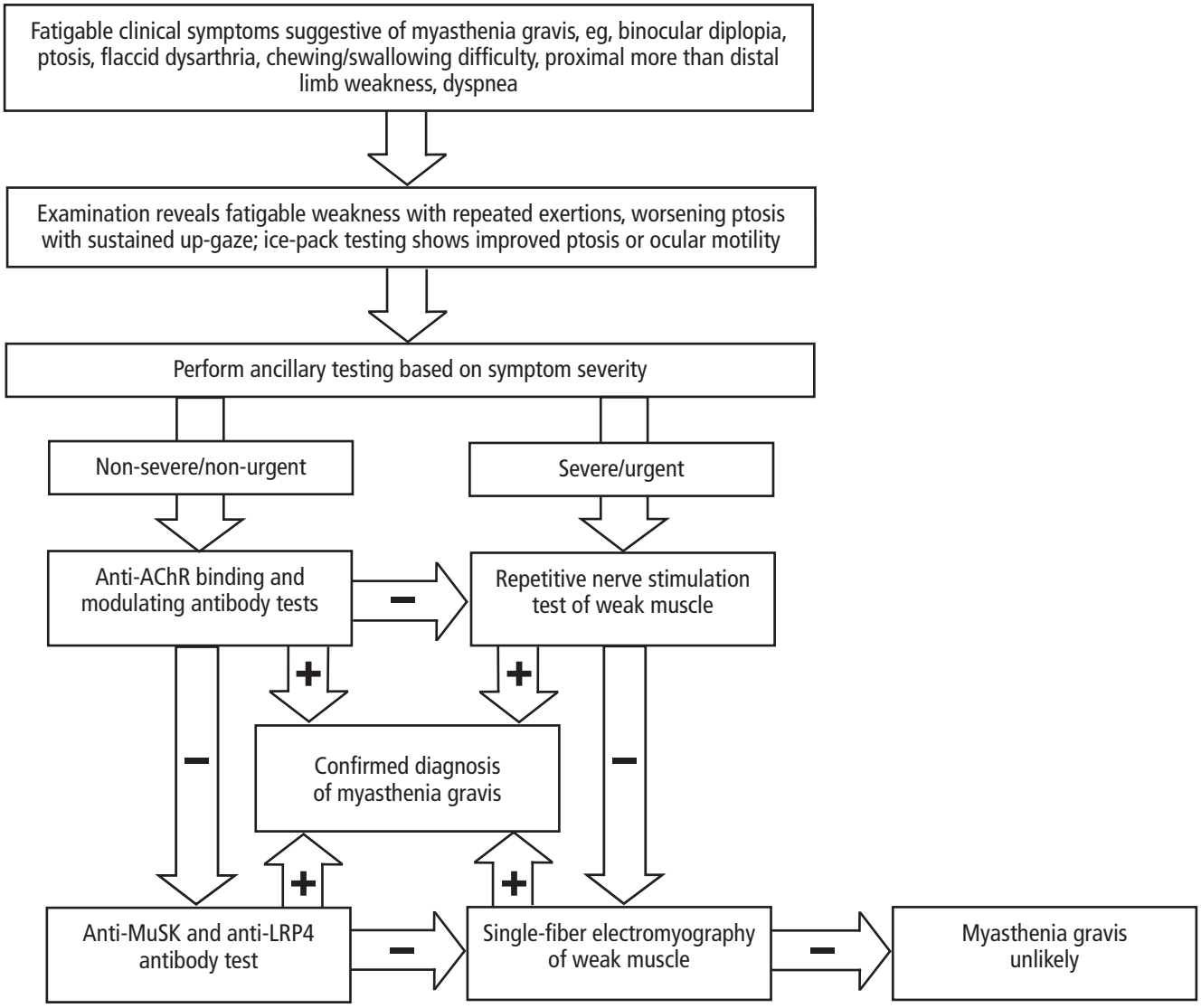


**Figure 1.** Diagnostic algorithm for myasthenia gravis. If the anti-AChR binding and modulating antibody tests are negative, two options are reasonable, as indicated.

AChR = acetylcholine receptor; LRP4 = lipoprotein-related protein 4; MuSK = muscle-specific tyrosine kinase

**Antistriated muscle antibodies.** On immunofluorescent staining, antistriated muscle antibodies bind in a cross-striational pattern to a number of muscle proteins including titin, ryanodine receptor, actin, myosin, tropomyosin, and filamin. They are much less specific for myasthenia gravis and are seen in about 30% of patients, and they are more useful as a marker for thymoma, especially in the nonelderly.[15] Thus, myasthenia gravis cannot be reliably diagnosed on the basis of positive antistriated muscle antibody alone.

## Electrodiagnostic tests

Two electrodiagnostic tests—repetitive nerve stimulation and single-fiber electromyography—provide objective evidence of impairment of neuromuscular junction transmission and are helpful in diagnosing myasthenia gravis. They need not be performed in

all patients, but they provide supportive diagnostic evidence, especially in seronegative patients and when prompt confirmation of the diagnosis is needed.

**Repetitive nerve stimulation** uses repeated "trains" of nerve stimulations to generate electrical muscle responses. The amplitudes of these responses can be measured to gauge the fatigability of neuromuscular junction transmission. The sensitivity and specificity of repetitive nerve stimulation depends on the nerve-muscle combinations examined, the severity of myasthenia gravis, and the cutoff values used for a decremental response. Its overall diagnostic sensitivity ranges from about 30% to 80% for generalized myasthenia gravis, with lower sensitivity in milder disease or when distal muscles are tested. In ocular myasthenia gravis, its sensitivity is only 10% to 30%.[16]

**Single-fiber electromyography** uses small needle electrodes to measure the variability of single muscle fiber potentials, a reflection of neuromuscular junction transmission. This test is often considered only when other diagnostic tests are unrevealing. It is more sensitive than repetitive nerve stimulation (62% to 99% for ocular myasthenia gravis, and 75% to 98% for generalized myasthenia gravis). Thus, a normal result in a clinically weak muscle essentially rules out myasthenia gravis. Its reported specificity varies from 66% to 98% for ocular myasthenia gravis and up to 98% for generalized myasthenia gravis, and abnormal results can be seen in other neuromuscular disorders such as motor neuron disease, congenital myasthenia gravis, or myopathy.[17]

### Other tests

Also useful in patients suspected of having myasthenia gravis are tests for common comorbid conditions, eg, chest computed tomography or magnetic resonance imaging for thymic abnormalities. One should be alert for clinical features that may suggest comorbid autoimmune conditions that would call for additional serologic tests such as thyroid-stimulating immunoglobulin, antithyroid peroxidase, antithyroglobulin, or rheumatoid factor.

## HOW DOES THE NATURAL COURSE AFFECT THE TREATMENT STRATEGY?

Myasthenia gravis tends to progress, especially in the first several years, so we recommend treating it aggressively with immunosuppressants at the outset and then gradually easing back.

Not until the late 1960s was myasthenia gravis recognized as an immune-mediated disorder, and immunotherapies such as corticosteroids, azathioprine, and methotrexate started to be used as treatments for it.[18] As a result, studies of its outcome done before the late 1960s generally reflected its natural course. In several such early studies, the mortality and morbidity rates were highest within the first 3 years of the disease and lower thereafter.[19–21]

In particular, ocular myasthenia gravis reaches its maximal severity within the first 3 years in most patients.[21] In older studies, approximately two-thirds of cases of ocular myasthenia gravis subsequently progressed into the generalized subtype, and of these, approximately 80% did so within the first year and 90% within the first 3 years.[21,22] In more recent series, the percentage of generalization from the ocular subtype was less, as low as 20%[23] to 50%.[24]

**Myasthenia gravis tends to progress, especially in the first several years, so we recommend treating it aggressively with immunosuppressants at the outset and then gradually easing back**

More immunotherapies for myasthenia gravis are now available. However, the aforementioned studies of the natural course help guide the assessment of risks and benefits of immunosuppressive treatment. While the early goal should focus on aggressive treatment to improve the patient's functional status, care must be taken to avoid serious adverse effects from intense immunotherapy. Patients who endure the first 3 years with relatively good symptom control tend to have a higher chance of gradual improvement or a steady state and, less often, worsening of the disease.[21,25,26] An exception is in refractory myasthenia gravis, which accounts for approximately 10% of patients with generalized myasthenia gravis and can be associated with relapses and exacerbations late in the course.

In the long term, it is preferable to steadily minimize immunosuppression if the patient's condition remains stable, while watching for relapse or exacerbation. Approximately half of patients can achieve remission or minimal symptoms with low-dose immunotherapy.[26] However, clinicians should be cautious about discontinuing immunotherapy completely, as only about 10% of patients may achieve complete stable remission off immunotherapy.[27]

## WHAT INSTRUCTIONS SHOULD PATIENTS RECEIVE?

After myasthenia gravis is diagnosed, patients should be educated about its typical course and largely benign prognosis. Points to discuss include:

- Specific symptoms of the disease, including red flags
- The importance of the progressive trend of symptom severity and frequency, rather than their transient worsening
- Common triggers of exacerbation, such as heat, infection, surgery, pregnancy, emotional disturbance, and certain medications (see discussion below)[28]
- The intended medication regimen, particularly immunotherapy, and potential side effects, to ensure compliance.

**If a patient needs more than 240 mg of pyridostigmine per day, it is time to move on to immunotherapy**

Many patients with myasthenia gravis are cautious about physical exertion, fearing that exercise might worsen their symptoms. However, most can tolerate and benefit from some form of exercise. Patients with mild disease can participate in resistance and aerobic training. For those with severe symptoms, stretching exercises such as tai chi, yoga, and balance training are usually most appropriate. Simply being more active and reducing overall sedentary time are important.[29]

Fatigue is common, reported in approximately 80% of patients at some stage of their disease. It is important to recognize differences between fatigue and fatigable weakness, as fatigue does not call for escalating myasthenia gravis treatment. The cause of fatigue in myasthenia gravis is multifactorial and includes deconditioning, cognitive blunting, sleep disturbance, and weight gain. Management of fatigue may include regular exercise, sleep evaluation, psychotherapy, and cognitive behavioral therapy.[29]

## WHICH MEDICATIONS ARE BEST AVOIDED?

Because some medications can trigger or worsen myasthenic symptoms, all patients with myasthenia gravis, especially those with significant weakness, should be observed for increased weakness whenever a new medication is started. In principle, if a patient's condition deteriorates when given a new drug, the drug should be withdrawn. Drugs that are most clearly contraindicated in myasthenia gravis include telithromycin, intravenous magnesium, botulinum toxin, penicillamine, and immune checkpoint inhibitors (see discussion below).[30,31]

Other medications that can worsen the disease include fluoroquinolones, macrolide antibiotics, aminoglycoside, beta-blockers, chloroquine, statins, and iodinated contrast (mostly associated with a low overall risk of aggravating myasthenia gravis). Most patients with mild to moderate disease or in stable remission tolerate these drugs without ill effect. Some medications (eg, aminoglycosides) are probably best avoided, as many alternatives are available. More robust data are needed to ascertain and quantify the risk of myasthenia gravis worsening with the other medications mentioned above.

Immune checkpoint inhibitors, used to treat malignancies, have become the most common iatrogenic cause of myasthenia gravis. They include blockers of programmed cell death receptor 1 (nivolumab, pembrolizumab), programmed cell death ligand 1 (atezolizumab, durvalumab, and avelumab), and cytotoxic T cell lymphocyte-associated antigen 4 (ipilimumab).

Immune checkpoint inhibitors can exacerbate symptoms in patients with myasthenia gravis or cause de novo disease. Many patients who develop myasthenia gravis as a result of these drugs have elevations of creatine kinase and troponin due to coexisting necrotizing myositis and myocarditis. The range of these autoimmune complications is wide—mild and monophasic in some patients, fulminant and even fatal in others. Prompt recognition is critical, as the immune checkpoint inhibitor needs to be stopped promptly and immunotherapy added.[32]

## HOW SHOULD PYRIDOSTIGMINE BE USED?

Pyridostigmine, the most commonly used acetylcholinesterase inhibitor for symptomatic treatment of myasthenia gravis, is typically used alone in mild cases or in combination with immunosuppressants in more severe ones. However, its efficacy may be minimal in patients with long-standing or severe myasthenia gravis.

Pyridostigmine's onset of effect is 30 to 60 minutes after each dose, and its duration is 3 to 6 hours. It should be taken 30 minutes before meals if dysphagia is present. A typical starting dose is 60 mg every 6 hours during daytime.

Patients who awaken with morning weakness can take a 180-mg extended-release formulation before sleep. However, the response to this formulation varies due to erratic absorption.

The dosage of pyridostigmine can be titrated up to 240 to 360 mg daily, but side effects are more common at higher doses, and overdose may result in increased weakness.[33] In practice, if a patient needs more than 240 mg per day, it is time to move on to immunotherapy. Once myasthenia gravis is controlled with immunotherapy, most patients do not need pyridostigmine. In a 1973 study in animals, long-term acetylcholinesterase inhibitor treatment at high doses led to degeneration and dysfunction of the neuromuscular junction,[34] but clinical experience suggests that pyridostigmine is generally safe without significant long-term complications.

The most common side effects are gastrointestinal, eg, abdominal cramping, loose stool, and flatulence. Bradycardia, bronchospasm, increased sweating, excessive lacrimation, muscle twitching, and cramping are other effects.

To manage side effects, oral glycopyrrolate or hyoscyamine can be taken concurrently with pyridostigmine doses. Dosage adjustment may be required in patients with renal impairment. One should be vigilant for the development of bronchospasm in patients with asthma.

Patients with MuSK antibody-positive myasthenia gravis may not respond well to pyridostigmine or may develop profuse cramps and fasciculations, even with low doses, possibly owing to reduction of cholinesterase levels at the neuromuscular junction.[8]

## WHEN SHOULD CORTICOSTEROIDS BE USED?

According to consensus guidelines,[30] corticosteroids or nonsteroidal immunosuppressive drugs should be used in all patients with myasthenia gravis who have not met their treatment goals after an adequate trial of pyridostigmine.

Only 2 controlled trials have evaluated the efficacy of corticosteroids in generalized myasthenia gravis.[35,36] However, retrospective studies of oral steroids (prednisone or prednisolone) as the main myasthenia gravis treatment also provide evidence that these drugs are effective.[37] Corticosteroids help nearly all patients with all subtypes of myasthenia gravis, resulting in marked improvement in more than 80%. Their onset of action is relatively rapid, 2 weeks on average.

Outpatients with mild to moderate symptoms can start prednisone at 20 mg daily and gradually increase the daily dose by 10 mg every 1 to 2 weeks up to approximately 60 mg daily, titrating to clinical response. Other corticosteroids with proven efficacy in myasthenia gravis include methylprednisolone, given intramuscularly or intravenously, and oral dexamethasone.[37]

Some patients respond better than others to corticosteroids. Good responders have a smooth and consistent response to moderate or high corticosteroid doses and can be kept in remission with low doses (eg, 5 to 7.5 mg of prednisone daily) without the need for nonsteroidal immunosuppressive agents. The long-term risk of such low-dose prednisone therapy is considered minimal.[38] Data suggest that patients over age 40, and especially those over age 60, are more likely to be good responders compared with younger patients.[37]

**Corticosteroids help nearly all patients with all subtypes of myasthenia gravis, resulting in marked improvement in more than 80%**

When starting corticosteroids, be alert for corticosteroid "dipping," ie, an exacerbation in myasthenic symptoms, seen in up to half of patients and usually occurring within the first week of starting treatment. Most cases are mild, and the worsening does not lead to the need for intubation or assisted ventilation. Dipping does not predict a poor long-term response to corticosteroid therapy.[39] Titrating the dose upward more gradually appears to reduce the occurrence of corticosteroid dipping.[40]

Once significant improvement is seen after starting corticosteroid therapy, there is no need to wait for maximum improvement to occur before starting to taper these drugs. Weaning should be slow and usually starts after several weeks of high-dose therapy. Initial steroid tapering typically involves reducing the daily dose of prednisone by about 5 to 10 mg per month.

## WHEN SHOULD OTHER IMMUNOSUPPRESSIVES BE USED?

Nonsteroidal immunosuppressive therapies should be considered in the following situations:

- Lack of significant response to prednisone
- More than 1 relapse upon prednisone tapering
- Inability to wean prednisone to an acceptable minimal dosage
- Contraindications to prednisone such as morbid obesity, brittle diabetes mellitus, peptic ulcer disease, high risk for osteoporosis, or significant side effects from prednisone.

Nonsteroidal immunosuppressive drugs such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, and rituximab have

been extensively used in myasthenia gravis to spare the use of corticosteroids in some patients. Newer agents recently approved such as eculizumab, ravulizumab, and efgartigimod could also serve this purpose in selected patients.[41–43]

Other factors such as antibody status, comorbidities, desired time course of action, and physician or patient preference may modify the choice of nonsteroidal immunosuppressive therapy. Rituximab is particularly effective for MuSK antibody-positive myasthenia gravis.[8] Azathioprine, methotrexate, and mycophenolate mofetil may take 6 to 12 months to work, while the onset action of cyclosporine, tacrolimus, and rituximab is generally quicker. Several of these drugs can damage the bone marrow, liver, kidneys, and lungs, and the functional status of these organs may influence their usage.[44]

At times, nonsteroidal immunosuppressive therapy may also be given as the initial immunosuppressant for patients with mild disease who are content with a slow course of improvement. In patients with significant weakness who have contraindications to corticosteroids, intravenous immunoglobulin, efgartigimod, or plasmapheresis can be used in the beginning to expedite clinical improvement while allowing time for an alternative nonsteroidal immunosuppressive therapy to produce its therapeutic effect.[45]

Because of the delayed action of some nonsteroidal immunosuppressive therapies, prednisone should be started concurrently. However, in general, one should avoid combining more than 2 immunosuppressants (eg, prednisone and a nonsteroidal immunosuppressive drug) in view of increased risks of infection and other side effects. An exception is in refractory myasthenia gravis, which often requires intense immunotherapy with multiple agents.[46]

For patients who gain good control by taking the combination of prednisone and a nonsteroidal immunosuppressive drug, prednisone is usually tapered first. After prednisone is tapered off or reduced to an acceptable minimal dose, the nonsteroidal drug can be tapered next, but much more slowly, usually over years. In some patients, both prednisone and the nonsteroidal drug can be kept at low dosages for optimal disease control and to minimize the side effects of each while taking advantage of their different mechanisms of action.

## WHAT IS THE ROLE OF THE THYMUS? WHO SHOULD UNDERGO THYMECTOMY?

The thymus gland is essential in the development of central tolerance and T-cell differentiation, and thus likely plays an important role in the immunopathogenesis of myasthenia gravis.

In approximately 10% of patients, myasthenia gravis is a paraneoplastic manifestation of an underlying thymic neoplasm (usually thymoma, rarely thymic carcinoma). However, thymic lymphoid hyperplasia is seen in up to 65% of patients with myasthenia gravis.[47] Lymphoid hyperplasia consists of numerous lymphocytes, macrophages, and plasma cells, reflecting the autoimmunity underlying myasthenia gravis that often begins in the thymus gland.

There is also evidence to suggest that autoimmunity against acetylcholine receptor may be due to intrathymic "myoid" cells and medullary thymic epithelial cells that elaborate acetylcholine receptor or subunits of it on their cell surface.[48]

### Indicated in patients with thymic neoplasms, and those similar to patients in the MGTX trial

The decision to remove the thymus is often influenced by whether patients have thymomatous or nonthymomatous myasthenia gravis. Thymectomy is indicated in all patients with thymic neoplasms. Otherwise, candidacy for thymectomy depends on several factors including AChR antibody status, myasthenia gravis type, disease duration, and patient age.

Supportive evidence comes from the landmark Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX).[49] To enter that trial, patients had to meet the following criteria:

- Have generalized myasthenia gravis
- Be AChR antibody-positive
- Be within 5 years of symptom onset.

Thymectomy in similar adult patients age 50 or younger is likely to improve clinical outcomes and permit minimal pharmacotherapy, including immunosuppressant use and dosage.

The benefit of thymectomy in patients ages 51 to 65 is more equivocal, and thymectomy is generally avoided in patients over age 65, since the risk-to-benefit ratio is less favorable.

There is no significant evidence to support thymectomy in those with MuSK antibody-positive myasthenia gravis. However, most experts would also consider thymectomy for patients with generalized myasthenia gravis who are "triple seronegative" (without antibodies to AChR, MuSK, or LRP4). This appears to be supported by evidence of similar benefits in both AChR antibody-positive and AChR antibody-negative myasthenia gravis subgroups.[50]

Thymectomy for patients with strictly ocular myasthenia gravis is controversial.

Although the surgery employed in the MGTX trial was traditional extended transsternal thymectomy via a median sternotomy, this has largely been replaced by less invasive procedures including video-assisted and robotic-assisted thymectomy via a transthoracic approach, and extended transcervical thymectomy through a low horizontal neck incision. Retrospective studies have shown similar clinical outcomes from the different surgical techniques.[51,52] The major advantages of less invasive surgical approaches relate to their lower postoperative complication rates and shorter length of stay in the hospital.

## HOW CAN MYASTHENIC CRISIS BE PREVENTED, RECOGNIZED, AND TREATED?

A myasthenic crisis is a life-threatening worsening of myasthenia gravis-related respiratory or bulbar muscle weakness that is severe enough to necessitate intubation or mechanical ventilation, or both.[30] If a patient has marked dysphagia, managing saliva and other oropharyngeal secretions can become difficult and the risk of aspiration is high.

Key measures in preventing myasthenic crisis are consistent disease control (including adherence to the medication regimen and careful weaning from immunosuppressants) and avoiding triggers or precipitants.

### Recognizing myasthenic crisis

Most patients with myasthenic crisis do not present with respiratory insufficiency alone. Rather, neuromuscular respiratory weakness usually occurs in the context of already worsening generalized or bulbar weakness, or both. Therefore, clinical features indicating significant worsening deficits in these areas may provide warning signs.

Of note, classic features of respiratory distress such as use of accessory muscles of respiration may be blunted during a myasthenic crisis, so these should not be overly relied upon. Orthopnea is a more specific feature than dyspnea, indicating significant neuromuscular respiratory weakness (especially of the diaphragm). Significant weakness in neck flexors and shoulder external rotators also typically correlates with respiratory muscle weakness.[53]

A screening test that can be done at the bedside or over the telephone is the single-breath counting test.[54] The patient is asked to take a deep inspiration and on subsequent expiration count from 1 onwards at a routine speaking pace (about 2 counts per second) until they need to take another breath. Inability to count to 20 with a single breath indicates significant respiratory weakness.

However, more formal spirometric measures are ideal, and the "20-30-40 rule" should be kept in mind.[53] This means that patients should be admitted or transferred to the intensive care unit for airway and respiratory management if vital capacity falls below 20 mL/kg, if the maximal inspiratory pressure (also known as negative inspiratory force) becomes less negative than −30 cm $H_2O$, or if the maximal expiratory pressure falls below 40 cm $H_2O$. Intensive care may also be warranted if the values are falling quickly (> 30% over 24 hours). It is very important that spirometry be done with a well-fitting face mask instead of a mouthpiece when there is significant weakness of facial muscles (particularly orbicularis oris), causing poor seal.

Measures of oxygenation, including pulse oximetry and arterial partial pressure of oxygen, are less helpful than those for carbon dioxide retention because of the prevailing mechanism of ventilatory compromise.

**TABLE 2**
**Treatments on the horizon for myasthenia gravis**

| |
|---|
| **Complement inhibitor** |
| Zilucoplan |
| **Neonatal Fc receptor inhibitors** |
| Batoclimab |
| Nipocalimab |
| Rozanolixizumab |
| **B-lymphocyte depletion therapy** |
| Obinutuzumab |
| Ofatumumab |
| Ublituximab |
| Blinatumomab |
| Inebilizumab |
| **Cytokine inhibitor** |
| Tocilizumab |
| **Janus kinase inhibitors** |
| Ruxolitinib |
| Baricitinib |
| Tofacitinib |
| **Hematopoietic stem cell transplantation** |
| **Chimeric antigen receptor T-cell therapy** |

### Managing myasthenic crisis

Managing myasthenic crisis entails optimizing medical management of intercurrent medical illness (including infections), removing any culprit medications, and giving aggressive immunotherapies aimed at quickly improving neuromuscular junction transmission.

The main therapies are plasmapheresis (also known as plasma exchange) and intravenous immunoglobulin, but usually not both. Both plasmapheresis and intravenous immunoglobulin may begin to produce clinical improvements within several days. However, since their efficacy may start to wane within a few weeks, concomitant augmentation of baseline immunotherapy (eg, corticosteroids) is needed. Anticholinesterase medications are generally withheld during a myasthenic crisis, especially if the patient has to be intubated, since discontinuation will reduce oropharyngeal secretions and aspiration risk.

Although general principles of weaning and extubation apply to those intubated and mechanically ventilated for myasthenic crisis, one should be mindful of more specific considerations. In particular, there should be a consistent reassuring trend in oropharyngeal secretion clearance and pulmonary function parameters (vital capacity > 15 to 20 mL/kg, maximal inspiratory pressure more negative than –25 to –30 cm $H_2O$) before weaning and attempted extubation. The best approach utilizes daily spontaneous breathing trials after initiation of intravenous immunoglobulin or plasmapheresis treatment.[55] Persistent neck flexor weakness may indicate a lower likelihood of successful extubation.

## WHAT NEW TREATMENTS ARE ON THE HORIZON?

The complement inhibitors eculizumab and ravulizumab and the neonatal Fc-receptor blocker efgartigimod have been recently approved by the US Food and Drug Administration for treating AChR antibody-positive myasthenia gravis, and many newer treatments with various mechanisms of actions are being studied (**Table 2**). Several of them (including rozanolixizumab and zilucoplan) have had positive results in phase 3 trials.[56]

The newer immunotherapies are generally more selective in their immunologic targets than the older ones. Accordingly, they have the advantage of causing fewer adverse effects, including life-threatening infections. However, they are very expensive, and a major drawback is their "financial toxicity." For many patients, the older broad-spectrum immunotherapies will remain a key component of treatment due to lower cost, ease of use, and potential of inducing remission. Nonetheless, the pace of major therapeutic innovations in the field is unprecedented, and the future of myasthenia gravis treatment is promising.

## DISCLOSURES

Dr. Li reports consulting for ArgenX, Catalyst, Immunovant, and UCB; research as principal investigator for Alexion, ArgenX, Catalyst, Immunovant, and UCB; receiving grant support from ArgenX; serving as advisor or review panel participant for Immunovant; and membership on the Clinical Practice Scientific Advisory Board for Alexion. Dr. Morren reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

## REFERENCES


1. **Liu FC, Kuo CF, See LC, Tsai HI, Yu HP.** Familial aggregation of myasthenia gravis in affected families: a population-based study. Clin Epidemiol 2017; 9:527–535. doi:10.2147/CLEP.S146617
2. **Keesey JC.** Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004; 29(4):484–505. doi:10.1002/mus.20030
3. **Grob D, Brunner N, Namba T, Pagala M.** Lifetime course of myasthenia gravis. Muscle Nerve 2008; 37(2):141–149. doi:10.1002/mus.20950950
4. **Pakzad Z, Aziz T, Oger J.** Increasing incidence of myasthenia gravis among elderly in British Columbia, Canada. Neurology 2011; 76(17):1526–1528. doi:10.1212/WNL.0b013e318217e735
5. **Sanders DB, Raja SM, Guptill JT, Hobson-Webb LD, Juel VC, Massey JM.** The Duke myasthenia gravis clinic registry: I. Description and demographics. Muscle Nerve 2021; 63(2):209–216. doi:10.1002/mus.27120
6. **Nair AG, Patil-Chhablani P, Venkatramani DV, Gandhi RA.** Ocular myasthenia gravis: a review. Indian J Ophthalmol 2014; 62(10): 985–991. doi:10.4103/0301-4738.145987
7. **Finnis MF, Jayawant S.** Juvenile myasthenia gravis: a paediatric perspective. Autoimmune Dis 2011; 2011:404101. doi:10.4061/2011/404101
8. **Morren J, Li Y.** Myasthenia gravis with muscle-specific tyrosine kinase antibodies: a narrative review. Muscle Nerve 2018; 58(3): 344–358. doi:10.1002/mus.26107
9. **Phillips LH 2nd, Torner JC, Anderson MS, Cox GM.** The epidemiology of myasthenia gravis in central and western Virginia. Neurology 1992; 42(10):1888–1893. doi:10.1212/wnl.42.10.1888
10. **Oh SJ, Morgan MB, Lu L, et al.** Racial differences in myasthenia gravis in Alabama. Muscle Nerve 2009; 39(3):328–332.doi:10.1002/mus.21191
11. **Dresser L, Wlodarski R, Rezania K, Soliven B.** Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. J Clin Med 2021; 10(11):2235. doi:10.3390/jcm10112235
12. **Mao ZF, Yang LX, Mo XA, et al.** Frequency of autoimmune diseases in myasthenia gravis: a systematic review. Int J Neurosci 2011; 121(3):121–129. doi:10.3109/00207454.2010.539307
13. **Christensen PB, Jensen TS, Tsiropoulos I, et al.** Associated autoimmune diseases in myasthenia gravis. A population-based study. Acta Neurol Scand 1995; 91(3):192–195. doi:10.1111/j.1600-0404.1995.tb00432.x
14. **Carr AS, Cardwell CR, McCarron PO, McConville J.** A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol 2010; 10:46. doi:10.1186/1471-2377-10-46
15. **Beloor Suresh A, Asuncion RMD.** Myasthenia Gravis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; December 15, 2021.
16. **Lamb CJ, Rubin DI.** Sensitivity and specificity of repetitive nerve stimulation with lower cutoffs for abnormal decrement in myasthenia gravis. Muscle Nerve 2020; 62(3):381–385. doi:10.1002/mus.26999
17. **Morren JA, Levin KH, Shields RW.** Diagnostic accuracy of single fiber electromyography for myasthenia gravis in patients followed longitudinally. J Clin Neurophysiol 2016; 33(5):469–474. doi:10.1097/WNP.0000000000000285

18. **Keesey J, Aarli J.** Something in the blood? A history of the autoimmune hypothesis regarding myasthenia gravis. J Hist Neurosci 2007; 16(4):395–412. doi:10.1080/09647040600675322
19. **Simpson JA.** An evaluation of thymectomy in myasthenia gravis. Brain 1958; 81(1):112–144. doi:10.1093/brain/81.1.112
20. **Oosterhuis HJ.** The natural course of myasthenia gravis: a long term follow up study. J Neurol Neurosurg Psychiatry 1989; 52(10): 1121–1127. doi:10.1136/jnnp.52.10.1121
21. **Grob D, Arsura EL, Brunner NG, Namba T.** The course of myasthenia gravis and therapies affecting outcome. Ann N Y Acad Sci 1987; 505:472–499. doi:10.1111/j.1749-6632.1987.tb51317.x
22. **Monsul NT, Patwa HS, Knorr AM, Lesser RL, Goldstein JM.** The effect of prednisone on the progression from ocular to generalized myasthenia gravis. J Neurol Sci 2004; 217(2):131–133. doi:10.1016/j.jns.2003.08.017
23. **Mazzoli M, Ariatti A, Valzania F, et al.** Factors affecting outcome in ocular myasthenia gravis. Int J Neurosci 2018; 128(1):15–24. doi:10.1080/00207454.2017.1344237
24. **Peeler CE, De Lott LB, Nagia L, Lemos J, Eggenberger ER, Cornblath WT.** Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. JAMA Neurol 2015; 72(10):1170–1174. doi:10.1001/jamaneurol.2015.1444
25. **Mantegazza R, Beghi E, Pareyson D, et al.** A multicentre follow-up study of 1152 patients with myasthenia gravis in Italy. J Neurol 1990; 237(6):339–344. doi:10.1007/BF00315656
26. **Salins S, Teter B, Kavak K, Wolfe GI, Silvestri NJ.** Low-dose medication and long-term outcome in myasthenia gravis. J Clin Neuromuscul Dis 2016; 18(2):61–66. doi:10.1097/CND.0000000000000122
27. **Sanders DB, Evoli A.** Immunosuppressive therapies in myasthenia gravis. Autoimmunity 2010; 43(5–6):428–435. doi:10.3109/08916930903518107
28. **Gummi RR, Kukulka NA, Deroche CB, Govindarajan R.** Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve 2019; 60(6):693–699. doi:10.1002/mus.26689
29. **O'Connor L, Westerberg E, Punga AR.** Myasthenia gravis and physical exercise: a novel paradigm. Front Neurol 2020; 11:675. doi:10.3389/fneur.2020.00675
30. **Sanders DB, Wolfe GI, Benatar M, et al.** International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016; 87(4):419–425. doi:10.1212/WNL.0000000000002790
31. **Narayanaswami P, Sanders DB, Wolfe G, et al.** International consensus guidance for management of myasthenia fravis: 2020 update. Neurology 2021; 96(3):114–122. doi:10.1212/WNL.0000000000011124
32. **Dubey D, David WS, Reynolds KL, et al.** Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. Ann Neurol 2020; 87(5):659–669. doi:10.1002/ana.25708
33. **Maggi L, Mantegazza R.** Treatment of myasthenia gravis: focus on pyridostigmine. Clin Drug Investig 2011; 31(10):691–701. doi:10.2165/11593300-000000000-00000
34. **Engel AG, Lambert EH, Santa T.** Study of long-term anticholinesterase therapy. Effects on neuromuscular transmission and on motor end-plate fine structure. Neurology 1973; 23(12):1273–1281. doi:10.1212/wnl.23.12.1273
35. **Howard FM Jr, Duane DD, Lambert EH, Daube JR.** Alternate-day prednisone: preliminary report of a double-blind controlled study. Ann N Y Acad Sci 1976; 274:596-607. doi:10.1111/j.1749–6632.1976.tb47718.x
36. **Lindberg C, Andersen O, Lefvert AK.** Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. Acta Neurol Scand 1998; 97(6):370–373. doi:10.1111/j.1600-0404.1998.tb05968.x
37. **Morren J, Li Y.** Maintenance immunosuppression in myasthenia gravis, an update. J Neurol Sci 2020; 410:116648. doi:10.1016/j.jns.2019.116648
38. **Utsugisawa K, Suzuki S, Nagane Y, et al.** Health-related quality-of-life and treatment targets in myasthenia gravis. Muscle Nerve 2014; 50(4):493–500. doi:10.1002/mus.24213
39. **Pascuzzi RM, Coslett HB, Johns TR.** Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984; 15(3):291–298. doi:10.1002/ana.410150316
40. **Seybold ME, Drachman DB.** Gradually increasing doses of prednisone in myasthenia gravis. Reducing the hazards of treatment. N Engl J Med 1974; 290(2):81–84. doi:10.1056/NEJM197401102900204
41. **Howard JF Jr, Utsugisawa K, Benatar M, et al.** Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study [published correction appears in Lancet Neurol 2017; 16(12 ):954]. Lancet Neurol 2017; 16(12):976-986. doi:10.1016/S1474-4422(17)30369-1
42. **Vu T, Meisel A, Mantegazze R, et al.** Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. NEJM Evid 2022; 1(5). doi:10.1056/EVIDoa2100066
43. **Howard JF Jr, Bril V, Vu T, et al.** Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial [published correction appears in Lancet Neurol 2021; 20(8):e5]. Lancet Neurol 2021; 20(7):526–536. doi:10.1016/S1474-4422(21)00159-9
44. **Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ.** Treatment of myasthenia gravis. Neurol Clin 2018; 36(2):311–337. doi:10.1016/j.ncl.2018.01.011
45. **Nagane Y, Suzuki S, Suzuki N, Utsugisawa K.** Early aggressive treatment strategy against myasthenia gravis. Eur Neurol 2011; 65(1):16–22. doi:10.1159/000322497
46. **Mantegazza R, Antozzi C.** When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies [published correction appears in Ther Adv Neurol Disord 2018; 11:1756286418765591]. Ther Adv Neurol Disord 2018; 11:1756285617749134. doi:10.1177/1756285617749134
47. **Nishino M, Ashiku SK, Kocher ON, Thurer RL, Boiselle PM, Hatabu H.** The thymus: a comprehensive review [published correction appears in Radiographics 2017; 37(3):1004]. Radiographics 2006; 26(2):335–348. doi:10.1148/rg.262045213
48. **Hohlfeld R, Wekerle H.** Reflections on the "intrathymic pathogenesis" of myasthenia gravis. J Neuroimmunol 2008; 201–202:21–27. doi:10.1016/j.jneuroim.2008.05.020
49. **Wolfe GI, Kaminski HJ, Aban IB, et al.** Randomized Trial of Thymectomy in Myasthenia Gravis [published correction appears in N Engl J Med 2017; 376(21):2097]. N Engl J Med 2016; 375(6):511–522. doi:10.1056/NEJMoa1602489
50. **Guillermo GR, Téllez-Zenteno JF, Weder-Cisneros N, et al.** Response of thymectomy: clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. Acta Neurol Scand 2004; 109(3):217–221. doi:10.1034/j.1600-0404.2003.00209.x
51. **Meyer DM, Herbert MA, Sobhani NC, et al.** Comparative clinical outcomes of thymectomy for myasthenia gravis performed by extended transsternal and minimally invasive approaches. Ann Thorac Surg 2009; 87(2):385–391. doi:10.1016/j.athoracsur.2008.11.040
52. **Bachmann K, Burkhardt D, Schreiter I, et al.** Long-term outcome and quality of life after open and thoracoscopic thymectomy for myasthenia gravis: analysis of 131 patients. Surg Endosc 2008; 22(11):2470–2477. doi:10.1007/s00464-008-9794-2
53. **Dhar R.** Neuromuscular respiratory failure. Critical Care Neurol 2009; 15(3):40–67. doi:10.1212/01.CON.0000348809.76308.c0
54. **Kukulka K, Gummi RR, Govindarajan R.** A telephonic single breath count test for screening of exacerbations of myasthenia gravis: a pilot study. Muscle Nerve 2020; 62(2):258-261. doi:10.1002/mus.26987
55. **Wu JY, Kuo PH, Fan PC, Wu HD, Shih FY, Yang PC.** The role of non-invasive ventilation and factors predicting extubation outcome in myasthenic crisis. Neurocrit Care 2009; 10(1):35–42. doi:10.1007/s12028-008-9139-y
56. **UCB presents efficacy and safety results for zilucoplan and rozanolixizumab in generalized myasthenia gravis.** https://www.ucb.com/stories-media/Press-Releases/article/UCB-presents-efficacy-and-safety-results-for-zilucoplan-and-rozanolixizumab-in-generalized-myasthenia-gravis. Accessed January 11, 2023.


***Address:*** *Yuebing Li, MD, PhD, Neurological Institute, S90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; Liy@ccf.org*