National Consensus on the Diagnosis and Treatment of myasthenia gravis

Edited by

Acad. Prof. Iv. Milanov, MD, PhD, DSc and Assoc. Prof. M. Milanova, MD, DSc

Sofia 15.03.2021

At the initiative of:

Bulgarian Movement Disorders and Multiple Sclerosis Society

Bulgarian Society of Neurology

National Consensus on Diagnosis and Treatment of myasthenia gravis

Today, March 15, 2021, we, the undersigned experts, have reached a consensus on the diagnosis and treatment of myasthenia gravis:

Acad. Prof. Iv. Milanov .....

Acad. Prof. L. Traykov .....

Prof. Iv. Tournev .....

Prof. V. Bojinova .....

Prof. D. Maslarov .....

Prof. A. Kaprelyan .....

Prof. L. Haralanov .....

Prof. K. Genov .....

Prof. P. Atanasova .....

Assoc. Prof. M. Milanova .....

Assoc. Prof. S. Ivanova .....

Assoc. Prof. N. Topalov .....

Assoc. Prof. M. Danovska .....

Assoc. Prof. D. Bogdanova .....

Myasthenia gravis is a neurological disease that is rare in general practice and this complicates its diagnosis and treatment. Although there is widespread agreement on the use of many drugs for the treatment of myasthenia gravis, there is no internationally accepted standard for this. As myasthenia gravis is a heterogeneous disease, there is no best therapeutic approach for all patients. The few randomized trials in these patients have limited generalization. Uncontrolled studies are of limited significance. This consensus is in line with international recommendations and guidelines, as well as our personal experience, and aims to guide clinicians on the approach to the diagnosis and treatment of myasthenia gravis.

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies against acetylcholine receptors (AChR), muscle-specific tyrosine kinase (MuSK), and other AChR-associated proteins in the postsynaptic membrane. It is characterized by rapid fatigue of the striated muscles and muscle weakness due to impaired transmission of nerve impulses at the level of the neuromuscular synapse.

The prevalence is about 15-25/100,000, with an annual incidence of 1 per 100,000 population. The onset of the disease in the anti-AChR form is bimodal - with an early peak about the age of 30 and late - about the age of 70-80. In Europe, most patients start complaining after the age of 50. In myasthenia with an early onset, the ratio of women to men is 3:1, while in myasthenia with a late onset, men suffer more often. Environmental factors are still poorly investigated. MG with anti-MuSK antibodies has a geographical difference in Europe with a characteristic south-north gradient - most cases are observed in the Mediterranean, and the least in the Scandinavian countries.

The etiology is related to the influence of genetic and environmental factors. Evidence of this is the concordance of 35% in monozygotic and 5% in heterozygous twins for the development of MG. Numerous genes have been identified, including HLA genes, responsible for the increased risk of developing MG. While some of them lead to various autoimmune diseases, others are more specific to MG and certain types of MG. Sex hormones also play a role in the predisposition to MG. They may also explain the different sex distribution of early-onset and late-onset myasthenia gravis and the higher prevalence of the disease among young and postpartum women. The role of various viruses attacking the thymus has been suggested. Some immunotherapies against tumors, as well as other autoimmune and rheumatic diseases, can induce myasthenia gravis.

The pathogenesis is autoimmune, involving the thymus gland. Disorder of neuromuscular transmission is associated with a significant reduction in the amount of acetylcholine receptors in the postsynaptic membrane of the neuromuscular synapse. The

damage is due to an antibody-mediated and complement-dependent autoimmune response with antibody production. The latter can be divided into two major groups - antibodies to transmembrane or extracellular proteins and intracellular. The first group of antibodies directly pathological for MG (as anti-AChR antibodies) or indirectly (as anti-MuSK antibodies and anti-lipoprotein bound peptide 4 (LPR4) antibodies) affect the function of AChR in the neuromuscular synapse, leading to impaired ion transport through the muscle membrane and reduced muscle contraction. Antibodies to intracellular proteins (titin, ryanodine receptors, cortactin) are unlikely to be pathological for MG, but can be used as a clinical marker to determine disease severity, the presence of thymoma, or myopathy. Due to their high specificity, the latter are not present in clinical practice.

Subgroups of myasthenia gravis

Early-onset myasthenia gravis

Patients with this form account for about 20% of all patients. The ratio of men to women is approximately 3:1. This form is associated with HLA-B8, DR3 and other autoimmune gene risk loci. Anti-AChR antibodies are present in them. Patients with thymoma are excluded from this group. Thymic follicular hyperplasia is possible.

Clinically, the first symptoms occur before the age of 50. Generalized muscle weakness is characteristic, and the whole clinical picture develops in the first three years of the disease. Comorbidity with other autoimmune diseases is also characteristic.

Late-onset myasthenia gravis

Patients with this form represent about 40% of all patients. Anti-AChR antibodies are available. The disease is more common in men and shows a weak association with some HLA genes (B7, DR2). Thymic pathology is rare, which is why patients do not respond to thymectomy.

Clinically, the first symptoms occur after the age of 50. Generalized muscle weakness is characteristic, and the whole clinical picture develops in the first three years of the disease.

Myasthenia gravis associated with thymus

This form is considered a paraneoplastic disease. Thymoma occurs in 10-15% of patients with myasthenia gravis. It is common in all ages with the same gender distribution. Myasthenia gravis is the most common autoimmune disease associated with thymus. Myasthenia gravis develops in 30% of patients with thymus. Anti-AChR antibodies and a

generalized form of the disease are observed in almost all patients. In the presence of thymoma, different types of antibodies can be detected. In the serum of about 30% of patients positive for anti-AChR, anti-titin antibodies are also detected. They are present in up to 85% of patients with thymus-associated myasthenia gravis. Anti-ryanodine antibodies are detected in 70% of patients with anti-AChR and thymoma. Anti-cortactin antibodies are found in 20% of patients without anti-AChR and MuSK antibodies, and in 5% of patients with anti-AChR. In routine practice, these antibodies are not tested.

Myasthenia gravis associated with anti-MuSK

MuSK is a protein that is expressed in the postsynaptic muscle membrane and is involved in maintaining AChR function. About 1-10% of patients with MG have anti-MuSK antibodies. Anti-MuSK and anti-AChR antibodies are rarely observed in the same patient. Thymic pathology was not observed in these patients and therefore they are not indicated for thymectomy.

Clinically, patients show affecting mainly of the bulbar and cranial muscles. About 1/3 of the patients have ptosis and diplopia. In more than 40% of the patients, bulbar weakness is observed as the first symptom and facial, pharyngeal and tongue weakness can be detected, along with weakness in the neck and respiratory muscles. The limbs are rarely affected.

Myasthenia gravis associated with anti-LRP4

It is more common in women. LRP4 is expressed in the postsynaptic muscle membrane and is a receptor that promotes the activation of MuSK, which is required for the maintenance of AChR function. Antibodies are detected in 2-27% of patients negative for anti-AChR and anti-MuSK. A study found anti-LRP4 antibodies in 15% of patients with anti-MuSK, in 8% of patients with anti-AChR antibodies and in 4% of patients with other neuroimmune diseases. In about 2/3 of the patients, the thymus is atrophic and normal for age, but cases of thymic hyperplasia have also been reported. In a small proportion of patients with myasthenia gravis, anti-agrin antibodies are detected, usually in combination with anti-MuSK or anti-LRP4 and rarely with anti-AChR.

Clinically, most patients have ocular or generalized muscle weakness. In about 20%, only eye weakness is observed.

Antibody-negative generalized myasthenia gravis

It is a heterogeneous group, with some patients having antibodies with low affinity or

low concentrations that are not detectable by current immune technologies. Some patients may have pathological antibodies to as yet unidentified antigens. In these patients, other diseases resembling myasthenia gravis should be ruled out.

Ocular myasthenia gravis

It occurs at any age, more often in women. Anti-AChR antibodies are observed in more than half of the patients, while anti-MuSK are rare.

Clinically, ocular muscle weakness is the most common initial symptom, but in only 15% of the patients the affect remains only in the eyes. Patients with an isolated ocular form have an increased risk of developing a generalized form of the disease.

The severity of myasthenia gravis is determined by the well-known in Bulgaria Ossermann scale, recently the clinical classification of the Myasthenia Gravis Foundation of America is more often used (Table 1).

Table 1. Myasthenia Gravis Foundation of America, MGFA Clinical Classification

Class I – Any ocular weakness

Class II – Mild generalized muscle weakness. May also have ocular muscle weakness of any severity

Class II a – Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both

Class II b – Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb and axial muscles

Class III – Moderate muscle weakness affecting other than ocular muscles. May also have ocular muscle involvement of any severity

Class III a – Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both

Class III b – Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles or both.

Class IV – Severe muscle weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity

Class IV a – Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both.

Class IV b – Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles or both.

Class V – Defined by oro-tracheal intubation, with or without mechanical ventilation, except when employed during routine postoperative care. The use of a nasogastric tube without intubation classifies the patient in Class IV b.

Diagnosis

Clinically, the main manifestation is the onset of rapid muscle fatigue during activity, most often affecting the muscles innervated by the cranial nerves (CN), trunk muscles and proximal muscles of the limbs. The external ocular muscles and the eyelid levator are most commonly and severely affected. Characteristically, ptosis of the eyelids and disturbance in the closure of the orbit (m. Orbicularis oculi) are observed equally, with preserved pupillary reactions to light and accommodation and the presence of diplopia due to fatigue of various muscle groups. Some clinical tests may be used to detect the ocular form of the disease:

- Strengthening of the posture (the curtain sign) - enhanced ptosis in the less affected eye, when raising the eyelid of the more affected eye
- Ice test - improvement of more than 2 mm in ptosis after 2 minutes of ice application on the orbit/eyelid

Muscle fatigue with reduced strength in the facial and masticatory muscles makes it difficult to eat and gives the face a characteristic hypomimic appearance, sometimes with adhesion of the lower jaw due to the impossible closing of the mouth. The phonation with nasal, broken to impossible speech, is disturbed. In more advanced cases, swallowing is difficult, often fluids come out through the patient's nose. Flexion of the neck is impossible spontaneously and against resistance, and patients often maintain the position of the head by helping with their hands. In the later stages, it is difficult to comb your hair, eat, talk, climb stairs and get out of bed.

Another characteristic clinical feature is the worsening of symptoms during the day due to fatigue of certain muscle groups - for example, the external ocular muscles when reading and watching TV, the phonation muscles after prolonged conversation or the proximal muscles of the limbs after physical activity. Some patients have worsening early in the morning, which is associated more with insufficient duration of the effect of the evening dose of a drug. At the beginning of the disease and in its milder forms, muscle fatigue is overcome relatively quickly after rest (Appendix 3).

No change is observed in reflex activity, sensory function, or heart and smooth muscle

activity.

Tests with anticholinesterase inhibitors (AHI - neostigmine, edrophonium) are performed after measuring muscle strength with dynamometry or vital capacity before and after administration of the respective drug. This test can be performed with neostigmine administered intramuscularly (1.5 mg) or slowly intravenously (0.5 mg). The improvement should be reported from the 15th minute to the 2nd hour after application. Premedication with atropine is desirable to prevent muscarinic effects. The improvement can be reported clinically, but it is better to confirm it electromyographically. A negative test does not rule out the presence of MG, but is a guide to looking for another cause of muscle weakness. Due to the presence of side effects in practice, a test with the use of 1 tablet pyridostigmine (60 mg) is used and reporting clinical improvement after 45-60 min.

Antibody titer should be tested in all patients with a clinical history suggestive of MG. In most patients, anti-AChR antibodies are observed, and if negative, anti-MuSKs are tested. As antibodies may not be detected initially and become positive subsequently, it is necessary to repeat the test after 6 months in the event of an initial negative result. Anti-AChR and anti-MuSK antibodies are very specific and in combination with an appropriate clinical examination practically diagnose myasthenia gravis. The accuracy of diagnosis of anti-AChR by immunoprecipitation method (RIPA) varies between 97-99%. They can also be found very rarely in patients with amyotrophic lateral sclerosis and in those with thymus present (these patients are at risk of developing MG). Anti-MuSK antibodies have never been found outside MG.

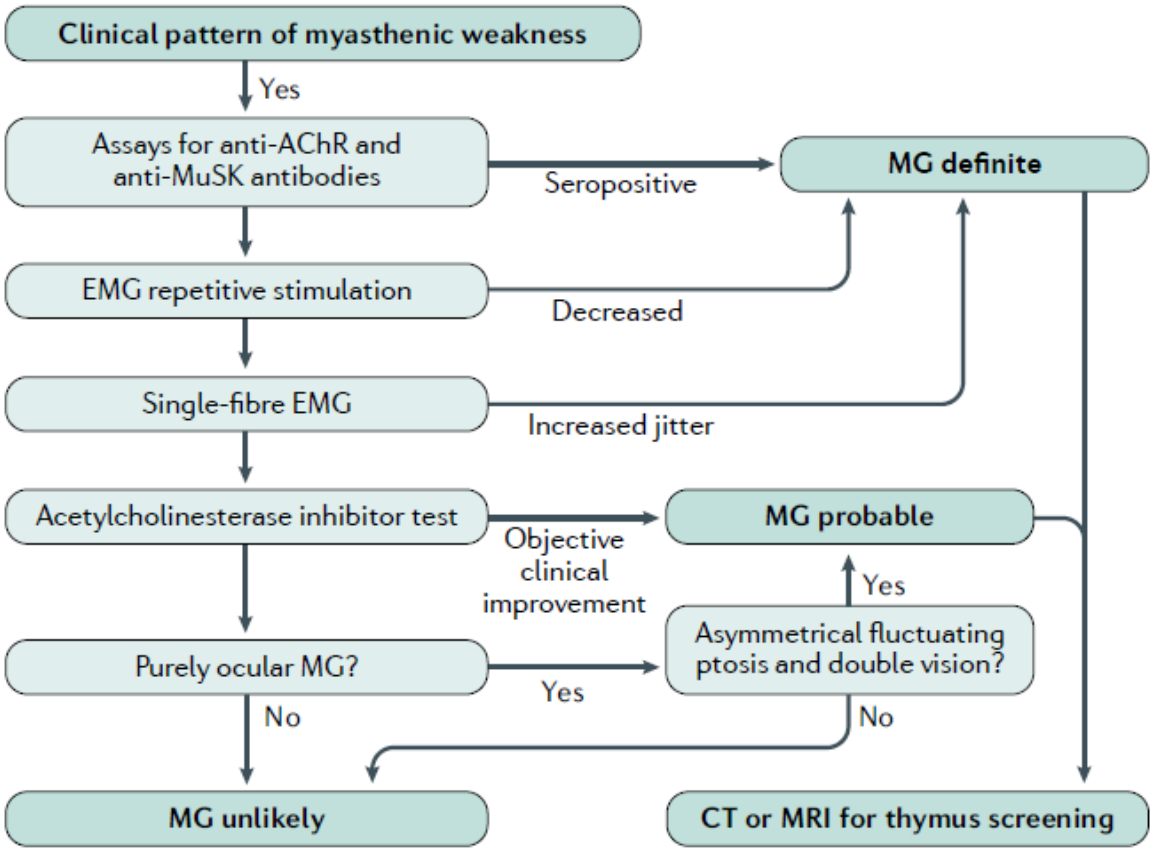
Electromyographic testing is the most commonly used method for detecting disorders in the neuromuscular transmission. It includes repetitive nerve electrostimulation (RNS) with low frequencies (1-3-5 Hz) and reporting of a typical decremental response (decrease in amplitude) of the compound motor action potential (CMAP). There is a positive decrement in up to 95% of cases with generalized myasthenia gravis and in 40% of patients with ocular form. Values above 10% amplitude decrease are considered a positive decrement (1:5).

A more sensitive and specific method for detecting subclinical disorders in neuromuscular transmission is single-fiber EMG. This method is positive in 96% of patients with generalized myasthenia gravis and in 80% of ocular cases. It evaluates neuromuscular jitter. In cases of myasthenia gravis it is abnormally increased, even in clinically unaffected muscle groups in which RNS does not show decrement.

CT of the anterior mediastinum to detect thymoma or thymic hyperplasia is essential

in diagnosis. The schematic algorithm for diagnosis of MG is presented in fig. 1

Fig.1. Algorithm for diagnosis of MG



Differential diagnosis

The diagnosis of MG in some cases can be very difficult due to the fact that a number of diseases occur with weakness of the muscles innervated by CN or the muscles of the body and limbs. In the course of some autoimmune diseases, MG can be included as an accompanying process, which complicates the diagnosis - for example, in hypo- and hyperthyroid conditions, lupus, etc.

Very often in the ocular form of MG it is necessary to exclude other causes leading to similar complaints - supranuclear disabilities in various diseases (progressive supranuclear external ophthalmoplegia, spinocerebellar and olivocerebellar atrophies, processes in the upper parts of the brainstem of various etiologies), ocular form of muscular dystrophy, multiple sclerosis, Guillain-Barre syndrome (oculopharyngeal and Miller-Fisher variant).

Congenital, genetically determined myasthenic syndromes, mitochondrial diseases and oculopharyngeal muscular dystrophy are also included in the broad differential diagnosis of MG.

In severe, mainly bulbar myasthenic involvement, it is necessary to make a differential diagnosis with processes that involve the brain stem - tumor, vascular, amyotrophic lateral sclerosis, etc.

Generalized weakness in MG is difficult to distinguish from similar symptoms in myopathies, polymyositis, hyperthyroidism, Guillain-Barre syndrome, porphyrin polyneuropathy, hyper- and hypokalemic periodic paralysis. For a correct diagnosis it is necessary to pay attention to the differences in reflex activity, sensory, paraclinic and electrophysiological findings.

Some toxic damages of neuromuscular transmission or peripheral nerves can mimic myasthenia gravis - diphtheria toxin, botulinum toxin, insecticides, antibiotics, snake and spider bites, plant D – tubocurarine, etc.

Organophosphorus substances used as pesticides irreversibly inhibit acetylcholinesterase. They are absorbed through the lungs, gastrointestinal tract and skin, then cause muscarinic and nicotine effects. In severe poisoning, depression of the respiratory center in the medulla oblongata occurs. After the acute toxic period in the next 24-96 hours, progressive muscle weakness is observed, and later distal axonal polyneuropathy develops, which is more pronounced for the legs than for the arms. The effects of all organophosphorus substances with the exception of neuro-paralytic gases are transient.

In *Lambert-Eaton syndrome*, there is also damage of neuromuscular transmission and a myasthenic pattern, which has typical clinical and electrophysiological differences from MG.

Treatment

It aims to achieve satisfactory control of symptoms and minimize the risk of side effects. This goal can be achieved through an individual therapeutic approach. MG is treated according to similar principles, largely regardless of antibody status. Treatment strategies can be divided into symptomatic treatment, which facilitates neuromuscular transmission, and immunosuppressive treatment aimed at the underlying pathological immune response (Fig. 2 and Fig. 3).

Fig. 2 Algorithm for treatment of MG

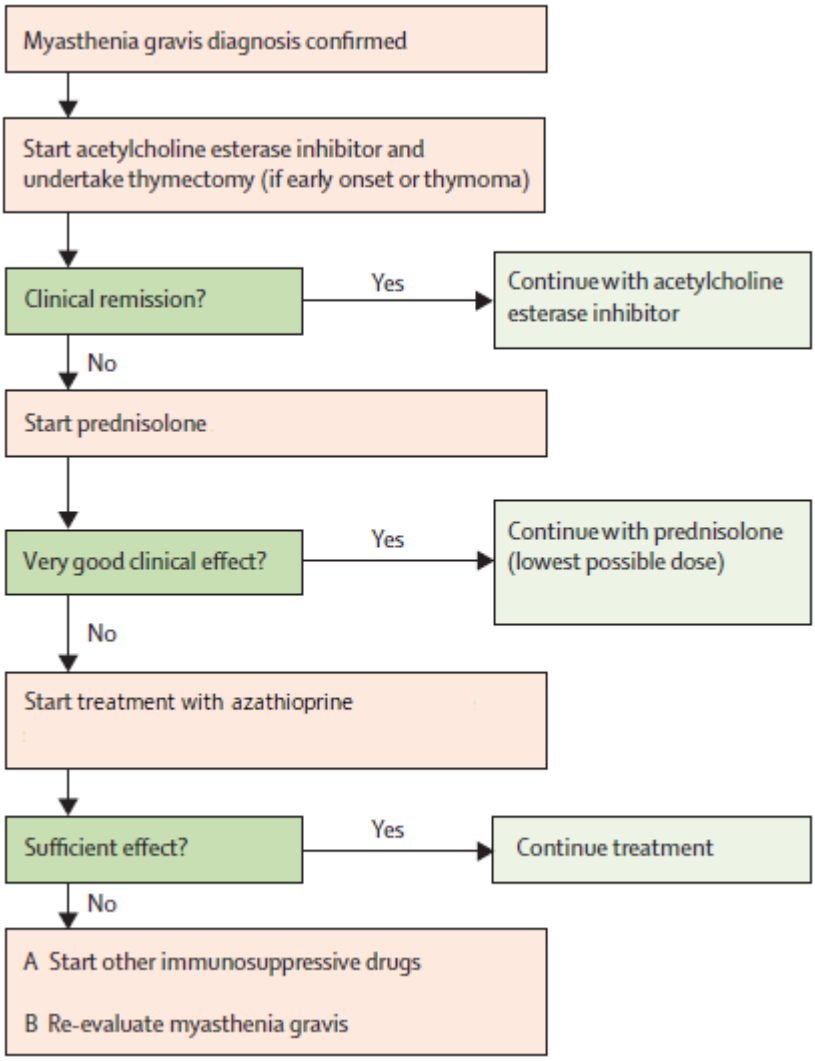


Fig. 3. Algorithm for treatment of generalized and ocular MG

Algorithm for treatment of generalized myasthenia gravis
1. Initiation of treatment with pyridostigmine
2. In patients with anti-AChR antibodies and under the age of 50, thymectomy should be considered.
3. If symptoms persist with pyridostigmine, treatment with corticosteroids is initiated.
4. If symptoms recur when the dose of corticosteroids is reduced to 7.5 - 10 mg/day (15-20 mg in an alternating regimen) or more, immunosuppressive therapy is initiated.
Algorithm for treatment of ocular myasthenia gravis

1. Initiation of treatment with pyridostigmine
2. If symptoms persist with pyridostigmine, treatment with corticosteroids is initiated.
3. If symptoms recur when the dose of corticosteroids is reduced to 7.5 - 10 mg/day (15-20 mg in an alternating regimen) or more, immunosuppressive therapy is initiated.
4. Thymectomy may be performed in patients with anti-AChR antibodies and ocular MG who do not respond adequately to pyridostigmine treatment and who are contraindicated or refractory to or refusing immunosuppressive therapy.

Symptomatic treatment

Anticholinesterase agents reversibly block the enzyme acetylcholinesterase and delay the hydrolysis of acetylcholine. Pyridostigmine (Mestinon, Kalymin) is most often used in practice. *Pyridostigmine* is the drug of choice for the symptomatic treatment of MG, especially in the early stages of the disease and in mild, especially ocular forms of MG. The usual dose of pyridostigmine is 30 mg to 90 mg every 4-6 hours. The drug is titrated to the lowest effective dose. At the beginning of treatment and in milder forms it can be started with 30 mg (1/2 tablet) 3-4 times a day, then it can be increased to 60 mg (1 tablet) 4 times a day and when needed up to 90 mg 4-5 times a day. The effect of the drug begins after 20 minutes with a maximum in the first hour and lasts 3-4 hours. In case of insufficient effect, the single dose may be increased or the interval between doses may be shortened. The maximum single dose at longer dosing intervals is 180 mg. For the evening intake it is permissible to use tablet forms with controlled release (not available in Bulgaria). If the dose is increased, there is a risk of side effects on both nicotine and muscarinic receptors. Such side effects rarely occur at doses below 300 mg/day. The most common muscarinic events are intestinal hypermotility (stomach cramps, diarrhea), increased salivation, increased respiratory and gastrointestinal secretion and bradycardia. The main nicotine side effects are muscle fasciculations and cramps. Cholinergic crises with severe clinical impairment are rare today due to the early inclusion of immunosuppressive therapy, which reduces the need for high doses of symptomatic treatment. In patients with anti-MuSK MG, anticholinesterase treatment is not recommended due to ineffectiveness and increased risk of adverse events.

Immunosuppressive treatment

It is used in all patients in whom a satisfactory result of anticholinesterase treatment has not been achieved. Corticosteroids and azathioprine are the drugs of choice for immunosuppression in patients with MG. In case of contraindications, intolerance or

insufficient control of the disease at adequate doses of these drugs, other immunosuppressive drugs may be used. Second-line drugs are cyclosporin A, methotrexate, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide (Appendix 2).

Corticosteroid (CS) treatment is initiated when the effect of anticholinesterase alone or in combination with thymectomy is unsatisfactory. Corticosteroids act on the immune system by inducing T-lymphocyte apoptosis and suppressing the transcription of inflammatory cytokines. Studies have shown improvement in corticosteroid treatment in patients with ocular myasthenia gravis. There is evidence that treatment of ocular form with CS reduces the incidence of generalized disease. Corticosteroids may be administered in ascending or descending doses. In the first case, in the generalized form, it is started with 10-20 mg of prednisolone and the dose is gradually increased (10 mg per week or slower) to 60-80 mg once a day. In the alternating approach, a full-dose day and a low-dose day alternate (may be lower than the basic or zero). The maximum dose is maintained until the effect lasts for at least 2-3 months and is gradually reduced over months to the lowest effective dose. In the ocular form, the dose may be increased more rapidly (every 5 days) and symptoms are often controlled by lower maximum doses (50-60 mg). The reduction in corticosteroids is slower than the increase. An exemplary regimen for reducing corticosteroid treatment is to reduce the dose by 10 mg/month to 40 mg for the alternating day, then reduce by 5 mg/month to 20 mg for the alternating day, and then reduce by 2.5 mg/month to 10 mg on the alternating day. Below 10 mg on the alternating day, the reduction is made at 1 mg/month, until a maintenance dose of 7-8 mg is reached. The reduction may be alternating with zero or better with alternating higher and lower doses. The effect of corticosteroid treatment occurs in about a month (4-16 weeks) and improvement is found in about 70-80% of patients. High initial parenteral doses of methylprednisolone (100-120 mg urbason i.v.) may lead to initial worsening of symptoms and require monitoring in a hospital with the possibility of respiratory resuscitation. They are usually used for critically ill patients in combination with other therapeutic methods (plasmapheresis and/or immunoglobulins). In this case, after achieving a therapeutic effect, the dose is also reduced as described above. It is necessary to take into account the side effects of long-term corticosteroid treatment - acne, osteoporosis, weight gain, high blood pressure, gastrointestinal complications, development of diabetes, myopathy, cataracts, glaucoma, anxiety, depression, insomnia, psychosis and others. This necessitates systemic restriction of carbohydrates and salt, as well as the use of antacids, the use of vitamin D and bisphosphonates in patients receiving long-term corticosteroids. Alternatiing treatment with corticosteroids is not recommended in patients with diabetes mellitus, but daily, due to

better blood sugar control.

The use of immunosuppressive drugs concomitantly with corticosteroids is initiated in cases of corticosteroid adverse reactions considered significant by the patient or physician, inadequate response to corticosteroid therapy, or when reduction in corticosteroid therapy is not possible due to recurrence of symptom (over 15-20 mg maintenance corticosteroid therapy is considered an indication to initiate immunosuppressive therapy).

Azathioprine is a purine analogue that acts as a purine antagonist and inhibits DNA synthesis and cell proliferation. It is considered the immunosuppressive agent of first choice in patients with MG. It has been shown to be a steroid-sparing treatment in a randomized study. Treatment with it is started when CS cannot be reduced in safe doses or concomitantly with CS in patients at risk for side effects. It is started with 50 mg (1 tablet) once a day, then increased by 50 mg/week to 2.5 mg/kg/day. This dose is maintained for 10-12 months, after which it is gradually reduced to 1 mg/kg/day. The initial therapeutic response is observed after 4-12 months from the start of treatment with maximum effect after 6-24 months. There is evidence that the combination of CS with azathioprine is more effective, with longer periods of remission and fewer side effects than monotherapy. Several studies have shown efficacy and a reduced risk of progression in the treatment of ocular MG with azathioprine. Abrupt discontinuation of azathioprine treatment may lead to the onset or worsening of myasthenic symptoms, to the development of a myasthenic crisis, even in patients with complete or stable clinical remission. Some patients may have an intolerance to azathioprine, which occurs within the first 2 weeks of treatment with flu-like symptoms - fever, malaise and vomiting. Adverse events include leukopenia, anemia, thrombocytopenia and hepatitis, therefore it is necessary to examine the complete blood count and liver function before starting treatment, then weekly for the first 4 weeks, at 3 months in the first year, then every 6 months. Increases in liver enzymes return to normal after dose reduction, while persistent hepatitis or pancreatitis are indications for discontinuation of the drug. Azathioprine should be reduced when the white blood cell count falls below 4×10^9/L and stopped when it falls below 3×10^9/L. In patients starting azathioprine treatment, testing for a genetic variant of the enzyme thiopurine C-methyltransferase (TPMT), which inactivates azathioprin, is desirable. With a genetically low level of the enzyme, a severe myelosuppressive reaction is possible, so these patients should not be treated with azathioprin. Some patients, during long-term treatment with azathioprin, develop skin hyperkeratosis and skin tumors, which requires periodic assessment of the skin condition.

Cyclosporin is an immunosuppressive agent that suppresses T-cell function by

inhibiting calcineurin signaling. Its efficacy in the treatment of myasthenia gravis has been confirmed in a small randomized study, but further large-scale studies are needed. In a study, the group of patients treated with cyclosporin showed an improvement in muscle strength and a decrease in the titer of anti-AChR antibodies compared to a control group of patients. Treatment begins with doses of 3-5 mg/kg divided in two doses. Improvement with Cyclosporin treatment is seen more rapidly - most often within 4-8 weeks. Once achieved, the dose is reduced to 2-2.5 mg/kg in the two separate doses. There are more side effects from treatment compared to azathioprine. These include opportunistic infections, myelosuppression, gingival hypertrophy, gastrointestinal disorders, nephrotoxicity with hyperkalemia, and hypertension. Some specific side effects are tremor, lowered epileptic threshold and, rarely, the occurrence of reversible posterior leukoencephalopathy. This, together with the many interactions with other drugs, makes cyclosporin treatment limited to a small number of patients with MG, in case of failure of therapy with other drugs. Periodic monitoring with examination of leukocytes, liver and kidney function is desirable.

Mycophenolate mofetil is an immunosuppressive drug that inhibits purine nucleotide synthesis and selectively disrupts lymphocyte proliferation. Two randomized trials have not identified an additional benefit of Mycophenolate mofetil as monotherapy compared to prednisolone or as a steroid-sparing drug. The negative result is most likely due to the design of the studies, as many smaller others have reported it to be efficient in patients with myasthenia gravis, including therapeutically resistant course. The drug may be used in case of intolerance or lack of response during treatment with azathioprine. Treatment begins with doses of 500 mg/day with an increase to 1.5 g/day. Efficacy occurs after 2-3 months, with maximum benefit after 6-18 months. One study has found that Mycophenolate mofetil was also an efficient steroid-sparing agent in long-term treatment of ocular myasthenia gravis. The maintenance dose was 1 g/day. Adverse events are usually mild and myelosuppression and hepatotoxicity may occur rarely. It is desirable to monitor the complete blood count at the beginning of treatment, then weekly for four weeks, then twice a month for two months, then monthly for the first year and every 6 months thereafter.

Methotrexate is an immunosuppressant that inhibits the synthesis of DNA, RNA and proteins and reduces the proliferation of lymphocytes. Although studies on the efficacy of methotrexate in the treatment of myasthenia gravis are scarce, oral methotrexate can be used as a steroid-sparing therapy in patients with generalized myasthenia gravis who do not tolerate or respond to other steroid-sparing drugs with a better profile. Treatment with doses of 7.5-25 mg/week, in combination with folic acid, has been shown to be effective as second-line

immunosuppressive therapy for the treatment of myasthenia gravis. Due to fewer interactions with other drugs, methotrexate is preferred to cyclosporin in adult polymorbid patients.

Cyclophosphamide is a strong suppressor of B-lymphocyte activity and antibody synthesis, and in high doses has an effect on T-lymphocytes. A randomized study found a significant improvement in muscle strength and the use of a lower dose of corticosteroid in patients taking both medicines compared to a placebo group taking only a corticosteroid. Intravenous administration of cyclophosphamide allows a reduction in the dose of corticosteroids without deterioration in muscle strength. Due to the high risk of toxicity, including bone marrow suppression, opportunistic infections, bladder toxicity, risk of neoplasia, the drug is used in patients with myasthenia gravis who do not tolerate or do not respond to steroid therapy plus azathioprine, methotrexate, cyclosporin and mycophenolate mofetil.

Tacrolimus inhibits the proliferation of activated T-cells by calcineurin signaling (similar to the action of cyclosporin). Several studies have established a clinical benefit of the drug (3-5 mg/day) in the treatment of treatment-resistant myasthenia gravis. Due to their similar action to cyclosporin, side effects are also similar and highly dose-dependent. Tacrolimus is nephro- and neurotoxic and interacts with many other drugs.

Rituximab is an anti-CD20 monoclonal antibody that reduces B-lymphocytes. It is used in patients who are resistant to standard immunosuppression, in two regimens - 375 mg/m^2/week for four consecutive weeks or 1,000 mg on the first and fifteenth day. Most patients need more than 1 course of treatment. Due to the lack of an established protocol, the decision to repeat courses is made on the basis of clinical observation and study of the B-cell subpopulation. International guidelines are in favor of initiating early treatment with *Rituximab* in patients with anti-MuSK antibodies who have poor control after initial immunosuppression. Efficacy in studies in therapeutically resistant anti-AChR myasthenia gravis is uncertain, but treatment with *Rituximab* is considered an option if other drugs are not well tolerated or are not efficient enough. Three cases of progressive multifocal leukoencephalopathy have been reported in patients treated with Rituximab and prior immunosuppressive therapy with other drugs.

Eculizumab is a monoclonal antibody that binds to protein C5 and prevents the activation of the compliment. Randomized trials have found benefits in the treatment of patients with treatment-resistant myasthenia gravis. It is recommended to start treatment with Eculizumab, in therapeutically-resistant, with available anti-AChR antibodies, generalized myasthenia gravis, after failure of other immunosuppressive drugs. Before starting treatment,

it is desirable the patient to be vaccinated against meningococcal meningitis in no less than two weeks. Further studies are needed to establish the duration of therapy required to achieve and maintain clinical efficacy, as well as studies on non-therapeutically resistant myasthenia gravis (eg., disease crises, as a starting drug in therapeutically non-resistant MG).

Thymectomy should be performed in almost all patients with thymoma. All patients undergoing thymectomy should have stable control of myasthenic symptoms achieved perioperatively with proper treatment. In patients with generalized MG and available anti-AChR antibodies, aged between 18 and 50 years, thymectomy is desirable in the early stages of the disease, relying on improvement in clinical outcome and reduction in the need for immunosuppressive treatment, as well as the need for hospitalization in case of exacerbation of the disease. The benefits of thymectomy in patients over 50 years of age and a long-standing disease are still controversial. Some studies have found long-term benefit after thymectomy in patients with ocular myasthenia gravis and anti-AChR antibodies, as well as a reduction in the incidence of generalized disease. However, thymectomy is not recommended for ocular disease, except in selected patients with a treatment-resistant course. Data from literature among patients with anti-MuSK MG have not established benefits of thymectomy, therefore it is not suitable for them. A retrospective study showed similar results after thymectomy in a 3-year follow-up in patients with anti-AChR antibodies and in antibody-negative ones. Improvement or remission after thymectomy was achieved in 57% of antibody-negative and 51% of anti-AChR positive patients. Despite the lack of randomized trials, thymectomy can be performed in patients without found antibodies.

Transsternal access for thymectomy is widely used, but recently less invasive procedures such as thoracoscopic and robotic thymectomy have entered clinical practice. Recommendations are for the use of less invasive techniques, as they have proven similar results to the more aggressive ones. Thymoma removal is performed to remove the tumor and may not improve MG. The entire thymus gland must be removed along with the tumor. Further treatment of thymoma depends on the histological classification and the degree of surgical excision. Incompletely resected thymomas should be treated after surgery with an interdisciplinary approach to treatment (radiation therapy, chemotherapy). Palliative radiation therapy may be considered in elderly patients or polymorbid patients with thymoma with appropriate clinical status. Small thymomas can be followed without treatment unless they enlarge or become symptomatic.

Supportive measures. Despite the lack of convincing evidence in the literature, a positive effect on the disease from weight reduction and modification of daily activity is

assumed. A recent study showed good tolerance, improved quality of life and improved muscle strength in patients with mild disease undergoing controlled exercise compared to those undergoing standard treatment alone. Several reports have indicated the benefits of breathing muscle exercises. It is also important to talk to the patient about the nature of the disease, lifestyle changes, possible treatments, and the possible effects of medications and substances on the course of myasthenia gravis (medications that can worsen MG and alternative medications - Appendix 1).

New therapies. Although immunosuppressive agents are effective in most patients with MG, many of them are associated with long-term side effects, often unbearable for patients. On the other hand, it takes a long time to achieve efficiency. With advances in translational research and the possibility of developing new drugs, more targeted therapeutic agents are emerging that can change the future of MG treatment. Some of the drugs currently being studied include C5 terminal complement inhibitors, Fc receptor inhibitors, B-cell depletion agents (anti-CD19 and 20 and B-cell activating factor inhibitors), proteasome inhibitors, cytokine and T-cells based therapies (chimeric antigen receptor T-cell therapy), administration of subcutaneous immunoglobulin. Most of these new drugs have advantages over conventional immunosuppressive treatment for MG in terms of faster onset of action, favorable side effect profile, and potential for lasting and long-term remission.

Myasthenia gravis and pregnancy

The scientific literature is scarce and cannot provide a basis for recommendations based on clinical trials. Myasthenia gravis is not thought to worsen during pregnancy, but exacerbations are more common after birth. Myasthenia gravis is rare, which is why there is a lack of specific information about medications during pregnancy. Many of the data are extrapolated from studies on the use of immunosuppressants in other autoimmune diseases during pregnancy.

Before pregnancy, patients at childbearing age should consult their neurologist and receive information about treatment during pregnancy and possible side effects. It is optimal to plan the pregnancy with stabilized myasthenia. If thymectomy is considered, it is appropriate to perform it before pregnancy. The condition of the thyroid gland should be determined before pregnancy and euthyroid status should be achieved. Patients should be instructed not to discontinue current immunosuppressive therapy and pyridostigmine during pregnancy. When planning a pregnancy, it is appropriate to avoid drugs with known teratogenic effects (methotrexate and mycophenolate mofetil). If they cannot be stopped, it is

appropriate to give women information about the risk to the fetus and the need for contraception.

During pregnancy, treatment should be provided by an interdisciplinary team including a neurologist, GP, gynecologist and anesthesiologist. Pregnant women with stable myasthenia gravis most often have no deterioration during pregnancy and childbirth. Patients should be informed not to change their therapy and that the use of prednisolone, azathioprine, cyclosporine and pyridostigmine is safe for them and the fetus (Table 1). Corticosteroids are the immunomodulatory agent of choice. It is desirable to apply if necessary, only in the second and third trimester, in lower doses. In Europe, azathioprine is widely prescribed to pregnant women and it is the non-corticosteroid immunosuppressant of choice. In the United States, the same drug is considered high risk and is not used. Patients with unplanned pregnancies treated with methotrexate and mycophenolate mofetil should be aware of the teratogenic effects of the drugs and that they should not be stopped abruptly due to the risk of deterioration without avoiding their teratogenic effects.

Thyroid function should be monitored during early pregnancy, especially if not previously tested.

Pregnant women with MG should be closely monitored for infections, especially of the urinary tract, and if present, should be treated immediately with antibiotics. Patients and the treatment team should have a list available of medications that can worsen myasthenia gravis.

It is appropriate to perform a fetal scan at the 12th and 20th week of gestation. After the 24th week of gestation, the movements of the fetus should be monitored, and 2-4 weeks before birth, the size of the uterus should be determined - for polyhydramnios and fetal motility. In patients with MG, arthrogryposis is a rare complication of the fetus. In the presence of pregnancy with arthrogryposis, myasthenia gravis in the mother should be actively sought.

Table 1. Safety of drugs for the treatment of MG during pregnancy and lactation

Drug	Adverse events	Note	Use during pregnancy	Use in lactation
Pyridostigmine	Not reported	Usual use. More frequent doses can be discussed.	yes	yes
Prednisolone	There is no convincing data on maxillofacial malformations. Increased risk of	Use in the lowest possible doses. Active search for gestational diabetes.	yes	yes

	gestational diabetes, hypertension and infections			
Azathioprine	Leukopenia	Usual use. Monitoring of leukocytes and liver enzymes	yes	yes
Cyclosporine/ Tacrolimus	Increased risk of gestational diabetes with tacrolimus	Usual use. Monitoring of leukocytes, liver, creatinine and diabetes.	yes	yes
Mycophenolate mofetil	Teratogenic risk calculated up to 25%	Discontinuation of the treatment and start another one if possible before pregnancy. The drug should not be stopped abruptly in case of unplanned pregnancy.	no	unknown
Methotrexate	Teratogenic risk calculated up to 15 - 20%	The drug should not be stopped abruptly in case of unplanned pregnancy	no	no
Intravenous immunoglobulin	Not reported		yes	yes

Appropriate conditions for the *childbirth* should be provided with the possibility of intensive care for the mother and baby - gynecologist, anesthesiologist, neonatologist, neurologist should be available. In women with stable myasthenia gravis, vaginal delivery should be preferred. Cesarean section is performed only at obstetric indications. Women should continue to take pyridostigmine during childbirth. Patients taking steroids chronically (>7.5 and <15 mg) should receive a stress-dose of corticosteroid at childbirth.

Many anesthetics that are considered contraindicated can be used without difficulty with proper monitoring. However, when possible, epidural/spinal anesthesia is preferred to the general one. Standard practice for general anesthesia is introduction with thiopental or propofol, followed by depolarizing muscle relaxant for intubation. Anesthesia is maintained with inhaled anesthetics and opioids. Patients are very sensitive to non-depolarizing muscle relaxants, which should be administered at lower doses and avoided whenever possible. The use of magnesium sulphate for the prevention of eclampsia should be avoided. In the presence of eclampsia with seizures, magnesium sulphate should be used with caution and in the presence of intubation and ventilation conditions.

In patients with myasthenia gravis, it should always be borne in mind that there is a possibility of *transient neonatal MG*, regardless of the severity of the mother's disease. The disease is characterized by hypotension, muscle weakness, bulbar and respiratory failure,

which is why childbirth should be performed in clinics with the possibility of neonatal resuscitation.

After the childbirth.

The mother's condition should be closely monitored, as deterioration may occur after birth, especially during surgery or due to infection. Breast-feeding should be encouraged in patients with MG, which is not contraindicated when taking prednisolone, azathioprine and pyridostigmine.

The baby's condition can worsen hours to days after birth, with symptoms of transient neonatal myasthenia. The condition does not correlate with the severity of the mother's illness. It is appropriate to monitor the baby for bulbar and respiratory disorders for about 2-3 days. The children of mothers with MUSK form of MG should be monitored most closely, as they have the most serious disorders. The incidence of neonatal myasthenia is between 9 and 30%.

Treatment of neonatal myasthenia gravis is supportive - a nasogastric tube for feeding and taking pyridostigmine and adequate respiratory support. In more severe cases, the use of immunovenin may be considered. Transfusion therapy should only be used in exceptional cases in very severe cases. Conducting an EMG requires special skills and is difficult to apply, but remains the only method of diagnosis in the neonatal period.

Although neonatal myasthenia is generally transient, infants of mothers with antibodies to the fetal acetylcholine receptor may develop prolonged myopathy with velopharyngeal insufficiency.

Myasthenia gravis in childhood is rare (10% of all cases), more common in Chinese children, and in most cases the form remains ocular. The diagnostic process is the same as in adults, but there are more seronegative cases, which requires testing for antibodies or congenital myasthenic syndrome, although the latter was not detected after birth. Thymoma should also be sought in children, but it is a much rarer pathology at this age. Spontaneous remission is more common and an attempt should be made to save on immunosuppressant therapy if possible. Late malignant complications of azathioprine treatment are possible. In children with persistent symptoms despite optimal medical treatment, thymectomy may be considered.

Congenital myasthenic syndromes are a heterogeneous group of rare conditions that are characterized by myasthenic symptoms at birth, in early childhood, and later. Ptosis, ophthalmoplegia, bulbar dysfunction, stridor and, less commonly, respiratory failure are typical. The syndrome occurs due to various mutations in genes associated with acetylcholine receptor proteins, is not immunomediated and therefore does not respond to

immunomodulatory and suppressive treatment. The syndrome is difficult to diagnose and is the subject of the activities of highly specialized centers for neuromuscular diseases. Sometimes congenital myasthenia gravis occurs during pregnancy and after birth. The risk of transmitting the syndrome to the fetus is low and patients are treated as those with autoimmune myasthenia gravis.

Myasthenic and cholinergic crisis

Myasthenic crisis (MC) is a clinical diagnosis defined as the development of respiratory failure and the need for non-invasive or invasive ventilation in patients with MG. MC occurs in about 15-30% of patients with myasthenia gravis, most often in the first 2-3 years after diagnosis. Very rarely it can be the first manifestation of the disease. Physical and/or emotional stress is always identified as the cause of the crisis. More than 30% of crises involve an infection, most often a lung infection. In the second place, aspiration pneumonitis is found with impaired bulbar function and on the background of immunosuppression. Other causes leading to crisis are surgery, pregnancy, medication use, fever, poor control of the underlying disease, emotional distress. In patients with severe MG, the crisis may be caused by errors in treatment with corticosteroids and acetylcholinesterase inhibitors.

The ***threatening myasthenic crisis*** is defined as a rapid clinical deterioration of MG, which could quickly (days, weeks) lead to a crisis. The 'red flags' for a threatening myasthenic crisis are:

- Febrile condition with infection treated with antibiotics in the previous 2 weeks
- Reverse aspiration - excretion of food and fluids through the nose
- Difficulty swallowing - clearing the throat or coughing when eating
- Difficulty coughing
- Aphonic dysarthria - weakening of the voice when speaking and nasal speech
- Suspension of the head forward - pronounced weakness in the extensors of the neck
- Sagging of the lower jaw and new facial weakness
- Changes in respiratory parameters - e.g. vital capacity below 20 ml/kg body weight

A ***cholinergic crisis*** may develop due to overdose of treatment with corticosteroids and acetylcholinesterase inhibitors. In it muscle weakness and respiratory decompensation are accompanied by muscarinergic (miosis, bradycardia, diarrhea, nausea, increased salivation, red and warm skin) and nicotinergic (cramps, fasciculations) signs of overdose. Cholinergic

crises are much rarer than myasthenic crises and are not always clinically easily distinguished. Increased salivation, which is a major sign of the cholinergic crisis, can hardly be distinguished from the difficulty in swallowing secretions in MC. The neurological differential diagnosis of crises and other diseases leading to acute muscle weakness are summarized in Table 2.

Table 2. Differential diagnostic signs of MC and acute muscle weakness

Clinical evaluation	**Myasthenic crisis**	**Cholinergic crisis**	**Guillain-Barre syndrome**
External ophthalmoplegia	70%	-	Only in the Miller-Fisher variant
Pupils	Normal, reactive	Narrow, reactive	Normal, may be non-reactive
Ptosis	70-80%	-	+/-
Muscle weakness	100%	++	+++
Fasciculations of the limbs	no	+++	+/-
Knee reflex	++	++	-
Babinski reflex	-	-	-
Sensitivity	norm	norm	Sometimes impaired
Autonomic symptoms	- *	+++	+

* Patients with MC may have autonomic symptoms for other reasons - tachycardia in sepsis, fever, hypoxia.

Clinical evaluation	**Polymyositis**	**Botulism**	**Motor neuron diseases**	**Myelon diseases**
External ophthalmoplegia	-	++	-	-
Pupils	Normal, reactive	Dilated, non-reactive	Normal, reactive	Narrow, reactive
Ptosis	-	+/-	-	+/-
Muscle weakness	+++	+++	+++	+++

Fasciculations of the limbs	+	-	+++	+/-
Knee reflex	+	-	+++ or -	+++ or -
Babinski reflex	-	-	+	+/-
Sensitivity	norm	changed	norm	sensory level
Autonomic symptoms	-	+++	-	+

Crisis treatment

In the presence of 'red flags' for a threatening crisis and a dynamic worsening of symptoms, patients should be immediately hospitalized in intensive care units or clinics. The following should be closely monitored for swallowing and respiratory function:

- In case of difficulty in swallowing - placement of a nasogastric tube for feeding and medication.
- In the absence of severe dysphagia and initial respiratory decompensation, non-invasive ventilation may be attempted, which may save invasive ventilation in a large number of patients.
- The criteria for undertaking intubation and artificial lung ventilation are known to resuscitation specialists. However, the myasthenic crisis is a clinical diagnosis. In cases of myasthenia gravis, pulse oximetry and blood gas data are not sufficient to monitor the patient and determine indications for intubation, as the decrease in oxygen saturation and PaO_2, as well as the increase in $PaCO_2$, occur late in the course of the crisis. The presence of normal saturation and PaCO2 does not rule out a myasthenic crisis. Examination of the external parameters of respiration (vital capacity and negative inspiratory force) is recommended every 2 hours, but is difficult clinically feasible in an emergency and the recommendations are accepted in practice from studies in patients with Guillain-Barre syndrome. Due to the lack of clinical trials in patients with MC, these criteria are widely accepted in practice (Table 3). Some easier-to-use tests, such as the single-breath test, find practical application. With a single breath, the patient is forced to count, with normal values up to over 40. Another option is to make the patient take a deep breath and hold it. Values below 10 seconds indicate significantly reduced vital capacity. Additional information is given by the deterioration of the respiratory rate, the respiratory effort with the participation of additional respiratory muscles and forced

position in bed. Examination of respiration, cardio-respiratory monitoring, neurological symptoms (eye movements, presence of dysphonia and dysphagia, weakness in the neck and limbs, fasciculations) and autonomic function (tachy- and bradycardia, arrhythmias, hypotension, hypertension, sweating) form the final picture. of the myasthenic crisis.

- When intubated, additional muscle relaxation is avoided if possible. In times of crisis, depolarizing muscle relaxants should be avoided, as the response to them is unpredictable. Doses of non-depolarizing relaxants are reduced to at least ½ than usual. In patients with MC, vigilant sedation with analgesia with propofol, fentanyl, remifentanil, benzodiazepines, lidocaine, or ketamine may be used.
- Ventilation modes - pressure breathing, early switching on of assisted pressure modes, obligatory synchronized volume modes are suitable.
- Commonly used in intensive therapy drugs that can worsen myasthenia gravis are aminoglycosides, quinolones, macrolides, anticonvulsants, beta-blockers, including topical, antiarrhythmic, muscle relaxants, contrasts, etc.
- Extubation is performed with stable parameters of external respiration and satisfactory cough function.
- An early tracheotomy is performed in the event of an expectant prolonged crisis.
- It is necessary to monitor the respiratory function - monitoring, radiography, the presence of delirium on the background of pulmonary ventilation.
- Treatment of concomitant complications - infections, electrolyte imbalance, hypoproteinemia, comorbidities, stress, immobility, stay in an intensive care unit.

Table 3. Parameters indicating the threshold for ventilatory support in MC

Criterion/test	**Norm**	**Need for intubation/ventilation**	**Extubation**
Vital capacity ml/kg body weight	>60 ml	<20 ml	>25 ml
Negative inhalation pressure cm H_2O	>60 cm	<20-30 cm	>40 cm
Positive expiratory pressure cm H_2O	>100 cm	<40 cm	>50 cm
Single inhalation test - counting	to 40-50	to 15-20	-

Treatment during MC and in case of threatening MC is multimodal and includes acute symptomatic and etiologic therapy, initiation of long-term immunosuppressive therapy, and intensive care (see above).

- *Acute symptomatic therapy* includes pyridostigmine tablets orally or by gavage 3-6 times 60-90 mg at a maximum dose of 540 mg daily. It can be replaced with intravenous pyridostigmine in a ratio of oral to 1:30 (not available in Bulgaria). Pyridostigmine may be replaced by neostigmine ampoules of 0.5 mg 1 ml as an oral dose of 360 mg pyridostigmine daily equals to 4.5 mg daily neostigmine intravenously or intramuscularly. Increased bronchial secretion from parenteral administration may be affected by 0.5 to 1 mg of atropine subcutaneously. In patients who have already been intubated, it is appropriate to stop cholinesterase therapy for a day or two.
- *Acute etiological therapy* of MC is mainly with plasmapheresis and intravenous immunoglobulins. There is currently no definite answer as to which of the two methods is more effective, with a slight tendency for a better and faster effect of apheresis in the presence of more risks (sepsis, difficult access) and difficulties in its application. The effect of both treatments occurs within days to a week, allowing other immunomodulatory therapies to take effect (Table 4). The course of treatment includes 5-6 plasmapheresis or 0.4 g/kg/day intravenous immunoglobulins for 5 consecutive days. Immunoglobulin treatment is not appropriate for patients with renal failure. In a threatening crisis, the dose of immunoglobulins can be reduced to 1.5 - 2 mg/kg/day for 2-3 days.
- *Intravenous pulse therapy* with methylprednisolone has been reported in some studies. The dose is 500-2000 mg/day for 3-5 consecutive days, followed by reduction according to different regimens. This treatment regimen may lead to a transient worsening of the myasthenic symptoms potentially inducing a myasthenic crisis due to a direct membrane effect of the corticosteroids. In addition, acute steroid myopathy may contribute to the overall deterioration of the clinic in this situation. We have no personal experience with this treatment regimen for MG and believe that it could only be used in overt myasthenic crises and in combination with plasmapheresis, immunoadsorption or intravenous immunoglobulin in an intensive care ward.
- *Long-term immunomodulatory therapy*
    1. Corticosteroids - initial worsening of symptoms may occur at the start of treatment, especially at higher doses. Therapy is conditionally divided into one in case of deterioration without respiratory failure and in case of crisis with artificial ventilation.

In the first case, the dose is increased in weekly increments from 10 mg prednisolone (equivalent to 2 tablets of other corticosteroids) to a total dose of 60 mg daily or alternating. Dose reduction is slower every 2-3 weeks with some doses being retained if necessary. In case of crisis and intubated patient, treatment can be started with high doses of corticosteroid - 100 mg prednisolone or 80-100 mg methylprednisolone, and the dose is reduced every 10-14 days to 20-40 mg, and later at longer intervals.

2. Azathioprine - starts with 50 mg per week in the first week, 100 mg in the second and up to 150 mg in the third week. Examination of lymphocytes, leukocytes and transaminases is required 6-8 weeks after the start of therapy and correction or discontinuation of treatment in case of abnormalities. In the presence of TPMT (thiopurine C-methyltransferase) deficiency, mycophenolate mofetil may alternatively be used.
3. Rituximab (there is no approval for this indication) - in case of unresponsive MC with optimal treatment, escalation therapy with rituximab 1 g twice every 14 days may be considered, and the dose may be repeated after 1 year or in case of an increase in CD19, as well as in the return of symptoms.

Table 4. Time necessary of therapies for myasthenia gravis to achieve effect

Type of therapy	Time to achive effect
Plasmapheresis/immunoabsorption	A few days
Intravenous immunoglobulins	A few days
Corticosteroids	One month - initial deterioration is possible
Azathioprine	6-12 months

Myasthenia gravis and Covid 19

Covid 19 is a new disease caused by a coronavirus (SARS-CoV-2), which causes severe acute respiratory syndrome. Symptoms vary in severity and include fever, cough, diarrhea, loss of taste and smell, respiratory decompensation. Currently, almost all countries in the world are affected by the disease and it has been declared a pandemic by the WHO. There are currently no data on how the virus affects patients with MG and those on immunosuppressive therapy. Theoretically, patients with MG are often on immunomodulatory and suppressive therapy and may develop respiratory muscle weakness, which would lead to a more severe course of infection.

There are many therapeutic recommendations for the treatment of Covid 19, which confuses practitioners. There are no systematic literature data on the treatment of MG and Covid 19, so it would be most reasonable to follow the national recommendations for the treatment of both diseases.

Treatment. Patients with MG should not discontinue their systemic treatment without a doctor's recommendation. This is especially true for pyridostigmine. If on immunosuppressive therapy, patients with MG should be particularly strict about social distance, including public transport and face-to-face medical examinations, if possible. When stopping immunosuppressive therapy, the benefits and risks should be weighed very carefully.

When administering immunoglobulin infusions and plasmapheresis, the risk of infection in hospital should be considered. There is currently no evidence that plasmapheresis and intravenous immunoglobulins carry an additional risk of Covid 19 infection. In general, these treatments should be reserved for patients with acute exacerbations and crises. As an exception, they can be performed as maintenance therapy, in the presence of contraindications for other types of treatment. There are currently no data that inhibition of the C5 fraction of complement with eculizumab may lead to more frequent infections and worse outcome in case of Covid 19.

Particular attention should be paid when it is necessary to start B-cell therapy (not available in Bulgaria) and if possible, in the absence of risk of crises, the onset should be postponed.

Covid 19 drugs (chloroquine, azithromycin, antivirals) have an unproven effect and are most often on the list of drugs that worsen MG.

Vaccination should not be given with live vaccines. According to the latest guidelines of the MGFA (Myasthenia gravis Foundation of America), currently available vaccines are safe to use.

If patients with MG are still infected with the virus, the current data show that the symptoms are usually mild and international and national guidelines for the treatment of MG should be followed. It may be necessary to increase the dose of corticosteroids. If patients have severe symptoms, they should be hospitalized and, in the presence of sepsis, immunosuppressive therapy may be temporarily discontinued. Standard treatment with azathioprine and mycophenolate mofetil may be continued as the dose effect is protracted and clearance of the drug would take a long time at risk of losing the immunosuppression that has been difficult to achieve for months. Dose reduction or increase of immunosuppressants should be carefully considered.

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Appendix 1 Medicines exacerbating myasthenia gravis - possible mechanisms of action and

their alternatives

Medicines exacerbating myasthenia	Alternative medicines
I. Antibiotics	
They disrupt neuromuscular transmission. The effect is possibly dose-dependent.	
Aminoglycosides: Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin **Penicillins:** with caution in severe myasthenia; Ampicillin - only under the supervision and evaluation of myasthenic symptoms **Quinolones / gyrase inhibitors** Ciprofloxacin, Levofloxacin, Enoxacin, Ofloxacin, Norfloxacin, Moxifloxacin **Carbapenems:** Imipenem + Cilastatin, Meropenem **Ketolides:** Telithromycin **Lincosamides:** Clindamycin, Lincomycin, Neomycin + Bacitracin, Erythromycin, Clarithromycin, Azithromycin, Roxithromycin **Tetracyclines:** Minocycline, Doxycycline (carefully with combined drugs) Metronidazole **Antimycotics:** Itraconazole, Fluconazol, Amphotericin B **Antimalarial drugs:** Proguanil Chinine Chloroquine	**Aminoglycosides:** Paromomycin **Cephalosporins:** Ceftriaxone, Cefalotin, Cefotaxime, Cefuroxime, Cefoxitin, Amoxicillin/Clavulanic acid, Kefandol, Cephalexin Chloramphenicol Nitrofurane Glykopeptide Teicoplanin Vancomycin Fosfomycin Oxazolidinone Linezolid **Sulfonamides:** from practice - possible problems with combined drugs: Sulfamethoxazole + Trimethoprim Trimethoprim – without problems with monotherapy, especially in urinary tract infections Rifampicin, Ethambutol Pyrimethamine + Sulfadoxin Streptogramine **Oxazolidines** Linezolid Aztreonam Atovaquone, Ketoconazole, Caspofungin, Nystatin, Terbinafine Mefloquine

Antiviral drugs: No worsening of myasthenia gravis has been observed **HIV antivirals: the same** **Anthelmintic drugs:** Pyrantel Pamoate	Acyclovir, Ganciclovir, Famciclovir, Valacyclovir Zidovudine, Lamivudine + Zidovudine, Abacavir, Efavirenz **Neuraminidase inhibitors drugs** Oseltamivir, Zanamivir (with other antiviral drugs, according to experience to date, there is also no risk of worsening myasthenia gravis) Mebendazol, Niclosamide, Praziquantel
II. Muscle relaxants	
Blocking neuromuscular transmission	
Suxamethonium, Gallamin, Chlormezanone, Dantrolene	Baclofen, Tizanidine Under anesthetic control and strict indication for sedation before anesthesia Tetrazepam **For relaxation:** Alcuronium chloride, Atracurium, Pancuronium bromide, Vecuronium bromide
III. Cardiovascular drugs	
Antiarrhythmics drugs: Blocking and/or inhibiting AChR receptors Sodium channel blockers Chinidine, Ajmalin, Procainamid, Lidocain, Propafenone, Mexiletine **Beta-blockers:** Propranolol, Metoprolol, Pindolol, Sotalol, Metoprolol, Atenolol, Bisoprolol, Oxprenolol, Carvedilol **Calcium channel blockers:** Nifedipine, Nisoldipine, Nitrendipine, Nimodipine, Amlodipine	Digitalis **ACE inhibitors:** Captopril, Lisinopril, Ramipril, Enalapril **Angiotensin receptor blockers:** Candesartan, Valsartan, Losartan **Centrally acting sympatholytics:** Clonidine, Moxonidin, α-Methyl Dopa, Reserpin-Mefrusid **Alpha-receptor blockers:** Prazosin, Doxazosin, Urapidil Phenoxybenzamine, Bunazosin Dihydralazin, Minoxidil, Na nitroprusside

Diuretics: Benzothiadiazine, Furosemid, Acetazolamide, Torasemide	Spironolactone Ethacrynic acid Piratenid
IV. Anticonvulsants + sedatives	
Benzodiazepines: Midazolam Diphenylhydantoin Ethosuximide Gabapentin Paraldehyde Magnesium sulfate	Carbamazepin, Oxcarbazepine Valproic acid Lamotrigine Levetiracetam Topiramat Pregabalin Primidone/ Barbiturates in low doses. There may be problems with high doses
V. Cholesterol and triglyceride lowering drugs	
Statins: *There is no evidence that they worsen myasthenia gravis*	Atorvastatin, Lovastatin, Pravastatin **Fibrates:** Bezafibrate, Etofibrat, Fenofibrate **Anion exchange resins:** Cholestyramine **Cholesterol absorption inhibitors:** Ezetimibe, Ezetimibe + Simvastatin
VI. Psychotropic drugs	
Reduce the synthesis and release of acetylcholine; impaired neuromuscular transmission	
Lithium carbonateHaloperidol Chlorpromazine **Tricyclic antidepressants:** Imipramine, Amitriptyline, Clomipramine **Benzodiazepines:** Lorazepam, Alprazolam Buspirone Droperidol Amphetamine	Levomepromazine Thioridazine **Tricyclic antidepressants:** Mianserin, Maprotiline hydrochloride, Trimipramine **Serotonin reuptake inhibitors:** Escitalopram, Citalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertraline **Also in low doses:** Chlordiazepoxide, Chloralhydrate, Mirtazapine, Reboxetine
VII. Antirheumatic drugs/Non-steroidal anti-inflammatory drugs	

Reduce the ability to bind acetylcholine. Decrease of membrane excitability	
Thiopronine Chloroquine D-Penicillamine Colchicine Quinine-containing medicines and beverages	Acetylsalicylate acid Indomethacine Diclofenac Ibuprofen COX-2 inhibitors
VIII. Antispasmodics	
The use of atropine in low doses is possible in severe cholinergic side effects or cholinergic crises N-Butyl scopolamine Bromide Oxybutynin Tolterodine Ipratropium bromide Chinine	Drofenin Papaverine
IX. Analgesics	
Morphine Flupirtin maleat Metamizol Propyphenazone (?) Codeine (?)	Acetylsalicylate acid Buprenorphine Hydromorphone Indomethacin Levomethadone Oxycodone Paracetamol Pethidine Piritramide Tolidine Tramadol
X. Eye drops (with caution in ocular myasthenia gravis)	
Beta blockers: Timolol, Betaxolol Guanidine sulfate Eye drops containing pilocarpine Caution with combined drugs containing	

corticosteroids and antibiotics!	
XI. Hormones	
Progesterone Contraceptives with estrogen + progesterone Corticosteroids Thyroid hormones	
XII. Antiparkinsonian drugs	
Muscarinic antagonists: Trihexyphenidyl Budipine Amantadine	L-Dopa **Dopamine agonists:** Bromocriptine, Lisuride, Pramipexole, Ropinirole Biperiden (?) Rasagiline, Rotigotine Entacapone
XIII. Other drugs	
Aprotinin Botulinum Toxin D, L-Carnitine Ciclosporin (?) very rarely Citrate-induced hypocalcemia for anticoagulation, e.g. in plasmapheresis Interferon Alpha 2b Interferon Beta 1b Contrast agents containing iodine Corticosteroids (under control due to risk of deterioration at the beginning of treatment) Medicines containing magnesium Nicotine patches Piperazine Pyrantel Pamoate Sleeping pills and tranquilizers: Zolpidem, Zopiclone Immune Checkpoint Inhibitors	

Appendix 2. Review of available immunosuppressive drugs for the treatment of myasthenia gravis

Drug	Mechanism of action	Side effects	Contraindications
Azathioprine	Purine analogue Inhibits DNA synthesis Reduces T- and B-cell proliferation	Increased liver enzymes, nausea, macrocytosis, pancreatitis, alopecia	Hepatic impairment, leukopenia, hematological malignancies or low thiopurine methyltransferase activity
Mycophenolate mofetil	Inhibits purine synthesis Reduces T- and B-cell proliferation	Nausea, diarrhea, leukopenia, increased liver enzymes, hypertension	Presence of tumor, leukopenia, before conception or during pregnancy
Cyclosporine	Calcineurin inhibitor Decreases IL-2 transcription Blocks T-cell activation	Nephrotoxicity, arterial hypertension, hypertrichosis, gingival hyperplasia, dizziness, headache, encephalopathy	Impaired renal function, severe arterial hypertension, presence of tumor
Tacrolimus	Calcineurin inhibitor. Decreases IL-2 transcription Blocks T-cell activation	Arterial hypertension, tremor, diabetes, nephrotoxicity, myocardial hypertrophy, encephalopathy	Renal impairment, severe hypertension, congenital long QT-interval syndrome, tumor
Methotrexate	Folate analog Disrupts DNA synthesis Reduces T- and B-cell	Stomatitis, nausea, hair loss, leukopenia, oligospermia, increased liver enzymes	Impaired liver function, bone marrow dysfunction, before conception or during pregnancy

	proliferation		
Cyclophosphamide	Alkalizing agent Disrupts DNA replication It suppresses more B- than T-cells	Nausea, vomiting, fever, hair loss, liver dysfunction, increased liver enzymes, cystitis, oligospermia, myelosuppression	Impaired liver function, bone marrow dysfunction, before conception or during pregnancy
Rituximab	Anti-CD20 monoclonal antibody Depletes B cells by cytotoxicity and provokes apoptosis	Infusion reactions, hypotension, leukopenia, mild infections, arrhythmias, dyspnea, reactivation of HBV, HCV and JCV, heart failure	Neutropenia, ischemic heart disease, congestive heart failure, before conception or during pregnancy

Appendix 3.

Scale for objective assessment of myasthenia gravis

Patient's name ----------

Age---------- Medicine---------- Physician ----------

Test	Score (Points)	Date and hour
Barré test (1 point for 10 s)	0-15	
Mingazzini test: (1 point for 5 s)	0-15	
Lifting the head: Impossible against own weight against resistance	 0 5 10	
Getting up from a lying position on your own: Impossible Possible	 0 10	
Oculomotor disorders: Diplopia Ptosis Norm	 0 5 10	
Closing the eyelids: Without covering the cornea By covering the cornea	 0 5	

Signe de cils Norm	7 10	
Chewing: Impossible Bad Norm	 0 5 10	
Swallowing: Impossible Bad Norm	 0 5 10	
Speech: Impossible nasal Norm	 0 5 10	
Medication		
Vital capacity		
Respiratory rate		