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Neurology Department

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Acronyms:

AChR	Acetylcholine receptor
ChEI	Choline esterase inhibitors
CMAP	Compound Muscle action potential
CT	Computerized Tomography Scan
EMG	Electromyography
GMG	Generalized myasthenia gravis
IVIg	Intravenous immunoglobulin
IS	Immune suppressants
MG	Myasthenia Gravis
MGFA	Myasthenia Gravis Foundation of America
MND	Motor Neuron Disease
MRI	Magnetic Resonance Imaging
MUAP	Motor Unit Action Potential
MuSK	Muscle specific tyrosine kinase
NCS	Nerve Conduction Study
NMJ	Neuromuscular junction
PLEX	Plasma exchange
OMG	Ocular myasthenia gravis
QMGS	quantitative myasthenia gravis score
RCT	Randomized Controlled Trials
RNS	Repetitive nerve stimulation
SFEMG	Single Fiber Electromypgraphy
SNAP	Sensory Action potential
SNMG	Sero-Negative Myasthenia Gravis

1. Definitions:

1.1 **Myasthenia gravis**: is a chronic autoimmune neuromuscular disorder resulting from an antibody-mediated neuromuscular transmission defect, where antibodies are directed against the muscle nicotinic acetylcholine receptors (AChR) or, sometimes against other post junctional components, such as the muscle specific kinase (MuSK) which indirectly decreases the AChR numbers.

1.2 **Remission:** The patient has no symptoms or signs of MG. Weakness of eyelid closure are accepted, but there is no weakness of any other muscle on careful examination. Patients taking cholinesterase inhibitors every day with reasonable evidence to support symptomatic benefit are therefore excluded from this category.

1.3 **Ocular MG** (based on dysfunction due to MG at a specified point in time and not dependent upon the duration of disease).

MGFA Class I: Any ocular muscle weakness. May have weakness of eye closure, while the strength in all other facial, bulbar, and limb muscles is normal.

It is recognized that some patients report fatigue when strength testing is normal. The physician should use clinical judgment in attributing fatigue to generalized MG in the absence of objective non-ocular weakness.

1.4 **Impending Myasthenic Crisis:**

Rapid clinical worsening of MG that, in the opinion of the treating physician, could lead to crisis in the short term (days to weeks).

1.5**Manifest Myasthenic Crisis** (the concept of crisis focuses on the clinical implications—it represents a serious, life-threatening, rapid worsening of MG and potential airway compromise from ventilatory or bulbar dysfunction).

MGFA Class V: Worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation, except when these measures are employed during routine postoperative management (the use of a feeding tube without intubation places the patient in MGFA Class IVB).

1.6 Refractory MG: Post-intervention status (PIS) is unchanged or worse after corticosteroids and at least 2 other IS agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician.

Guidelines for the Diagnostic Approach and Management of a Patient with Myasthenia Gravis

Chapter 1

2. Introduction:

Myasthenia gravis (MG) is a common chronic autoimmune neuromuscular disorder, characterized by varying degrees of fluctuating weakness and fatigability of the skeletal muscles. Although it is a potentially serious disorder, MG is treatable and the vast majority of patients improve with therapy over time. Some can often go into remission or minimal manifestation status. MG can be difficult to diagnose as symptoms can mimic variety of disorders; in addition to the fact that MG symptoms may be vague, fluctuate or only affect certain muscles in mild or early cases. Thus it is not unusual for a diagnosis of MG to be delayed or even misdiagnosed leading to unnecessary and potentially harmful therapeutic interventions, as well as to treatment delay and, hence, to increased morbidity. Therefore, it is critically important to have an accurate and early diagnosis; as well as a proper management.

3. Scope:

This guideline apply all neurology doctors working in neurology department at DGKH

4. Purpose:

The purpose for this guideline are to:

4.1 Improve quality of patient care and promote patient safety.

4.2 Provide a standardized approach to the management of patients with MG.

Chapter 2

5. Guideline:

5.1. Background:

a. Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder, characterized by varying degrees of fluctuating weakness and fatigability of the skeletal muscles without loss of reflexes or impairment of sensation or any other neurologic function. It is a relatively common neurological disease resulting from an antibody-mediated neuromuscular transmission defect. The disease can occur at any

age, however onset in the first decade is relatively rare (<10%) and it has two peaks for age of onset: between 20 -30 years in female and between 50-60 years in male.

b. The majority of patients present initially with ocular symptoms of fatigable ptosis and/or extra ocular muscle weakness causing diplopia (in up to 65% of patients) and resulting in ocular MG (OMG). Some progress to involve extraocular areas or present initially with increasing muscle fatigue, bulbar and/or proximal limbs' weakness causing generalized MG (GMG). Few patients may present with neuromuscular respiratory failure from the onset.

c. Despite the fact that the symptoms of MG are characteristic, they are common complaints which can be found in variety of medical and even psychological conditions; in addition, these symptoms are not specific to the condition. Hence, the diagnosis of MG can be difficult due to these facts, particularly in mild cases or when the physician is not familiar enough to suspect the condition. Moreover, it is realized that there is no single test that absolutely proves the diagnosis of MG and the combination of history, clinical examination, bed-side clinical testing (ice test and the Tensilon/Neostigmine test), electrophysiological investigations and serum anti-bodies tests often establishes the diagnosis beyond reasonable doubt.

d. In some cases all of these confirmatory tests are negative, although the clinical examination points to MG. In such cases, considered as "possible MG" or "probable MG", the patient would be monitored and followed up to check if the condition manifests itself and, sometimes, a diagnostic trial of treatment may be given.

5.2 Key Points:

a. A firm diagnosis prevents inappropriate treatments and their side effects, allows rapid implementation of MG-targeted treatment, and can redirect patients without MG for correct diagnosis.

b. Standardization of clinical assessment and the objective recording of clinical and laboratory findings contribute to improving the clinical diagnosis and characterization of MG, definition of subsets of the disease, evaluation and measuring of its clinical and functional features either at diagnosis or after treatment.

c. The diagnosis is based on clinical appraisal and confirmed by one or more pharmacological, electrophysiological, or serological tests. Imaging studies are essential to search for a thymoma.

d. There is no single test which could absolutely prove the diagnosis of MG and a combination of tests are used, with history and clinical examination.

e. Cholinesterase inhibitors, steroid and immunosuppressive treatment are effective in most cases and the response to plasma exchange and IVIg is often remarkable. Response to treatments may be helpful in confirming the diagnosis in those patients with undetectable autoantibodies.

5.3 Diagnostic Approach

Although the clinical information remains the 'gold or reference standard' used for the diagnosis of MG and for ruling out other disorders, bedside clinical, pharmacological and electrophysiological tests, as well as serum anti-bodies assay are used to confirm the neuromuscular transmission disorder, **See Appendix1: Figure 1- A Diagnostic Approach For MG**

5.3.1 Clinical Diagnostic criteria:

5.3.1.1 Inclusion: Characteristic signs and symptoms

a. Diplopia, ptosis, dysarthria, weakness in chewing, difficulty in swallowing, muscle weakness of limbs with preserved deep tendon reflexes, weakness of neck flexion and more rarely extension, weakness of trunk muscles, and respiratory symptoms with respiratory failure.
b. Increased weakness during exercise and repetitive muscle use with at least partially restored strength after periods of rest.
c. Clear improvement in strength following administration of a cholinesterase inhibitor (edrophonium or neostigmine).
d. Positive response to immunosuppressive treatment.
e. Dramatic improvement following plasma exchange or IVIg.

5.3.1.2 Exclusion/differential diagnosis :

a. Congenital myasthenic syndrome, myopathies (e.g. oculopharyngeal muscular dystrophy, mitochondrial progressive external ophthalmoplegia), steroid and inflammatory myopathies,
b. motor neuron disease

c. Eaton-Lambert syndrome
d. Multiple sclerosis (weakness with chronic fatigue or subacute/acute brainstem or spinal cord motor involvement)
e. Variants of Guillain-Barré syndrome (e.g., Miller-Fisher syndrome)
f. Organophosphate toxicity, botulism, black widow spider venom
g. Stroke
h. Hypokalemia; hypophosphatemia

5.3.1.3 Associations:

MG is often associated with:

a. Thyroid abnormalities
b. Other autoimmune diseases
c. Thymoma

5.3.2. Diagnostic testing

The diagnosis is based on clinical appraisal and confirmed by one or more pharmacological, electrophysiological, or serological tests. Imaging studies are essential to search for a thymoma.

5.3.3 Bedside clinical tests:

The Rest and ice pack tests are used to assess improvement in ptosis and diplopia in ocular MG.

a. Patients with ptosis are told to keep their eyes gently closed for two minutes. Approximately 50% of patients with myasthenia gravis will show an improvement in ptosis of 2mm or more with the rest test.
b. The ice test is performed by placing ice on the ptotic eyelid for two minutes and then re-evaluating the ptosis. Like the rest test, an improvement of 2mm or more is a positive test result
c. The rationale behind this test is that rest and cooling improve neuromuscular transmission by accumulating Acetylcholine within the synapse, improving muscle response.
d. Both the ice test and the rest test are sensitive and specific in ocular MG.

5.3.4 Pharmacologic Tests (Anticholinesterase test)

a. The strength of an involved group of muscles is assessed before and after administration of intravenous edrophonium chloride (Tensilon) or Neostigmine.
b. This test may give both false-negative results and false-positive results. It has a low sensitivity in ocular MG; 50% of patients presenting with eye symptoms will be missed. On the other hand, diseases such as amyotrophic lateral sclerosis (ALS) and cavernous sinus lesions can score positive on the test.

5.3.5 Serum antibodies assay and blood tests:

MG is an autoimmune disorder and is usually (80% of total MG patients) mediated by autoantibodies to the acetylcholine receptor (AChR, AChR-MG); in the 20% of patients that are not positive for AChR antibody, up to 50% have antibodies to muscle specific kinase (MuSK, MuSK-MG). The remaining patients are negative for both antibodies (SNMG), but evidence is accumulating which strongly indicates that other, as yet unidentified, autoantibodies are responsible for SNMG.

a. Antibodies tested:
    i. Anti-AChR antibodies assays are positive in as many as 90% of patients with generalized MG. The test is only positive in 50-70% of patients afflicted with strictly ocular MG. This test is highly specific
    ii. Anti-Musk antibodies, LRP4 Antibodies & anti striational Antibodies.
    iii. Several other antigenic targets have been reported in MG, although their pathogenicity, specificity for MG and diagnostic or prognostic value have not been fully characterized. These include the proteins agrin, Kv1.4 potassium channel, rapsyn, cortactin, acetylcholinesterase (AChE), collagen Q (ColQ) and collagen XIII.

b. Rheumatoid factor and antinuclear antibodies are indicated to rule out rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

c. Thyroid function tests are indicated to rule out associated Graves disease or hyperthyroidism. This is essential, especially in patients with ocular MG where the concomitant hyperthyroidism is most frequent.

d. CK, usually done to rule out ocular related myopathy disorder, especially in seronegative cases.

5.3.4 Electro-diagnostic testing

5.3.4.1 Routine Nerve conduction study (NCS) and Electromyography (EMG)

a. Routine motor and sensory nerve conduction studies (NCS) MG must not be omitted before embarking on electro diagnostic studies that demonstrate a defect of neuromuscular transmission.
b. Routine NCS is done to ensure the integrity of any nerve that subsequently will be used in RNS.
c. A decrement in Repetitive nerve stimulation (RNS) can be seen in other conditions (neuropathies, motor neuron disease, inflammatory myopathies) and myotonic disorders.
d. At least one motor and sensory conduction study should be performed in an upper and lower extremity.
e. Compound muscle action potentials (CMAP) amplitudes should be normal with only 3% to 15% showing CMAPs that are diffusely low. If CMAP amplitudes are low or borderline, repeat distal stimulation after 10 seconds of exercise to exclude a presynaptic NMJ transmission disorder such as LEMS.
f. The routine needle EMG of distal and proximal muscles, especially weak muscles may reveal unstable or small amplitude, short duration, polyphasic motor unit potentials, with or without early recruitment. Unstable motor units represent muscle fibers that are blocked or come into action potential at varying intervals, resulting in MUAPs that change in configuration from impulse to impulse.
g. Fibrillation potentials and other abnormal spontaneous activity are not seen in NMJ disorder, except in the case of botulism.

5.3.4.2 Repetitive nerve stimulation:

a. Repetitive nerve stimulation (RNS) should lead to a decremental response in compound action potentials on EMG.
b. A stimulation rate of 2-3 per second should result in a 10% or more decrease in amplitude by the fourth action potential
c. RNS results are less likely to be positive in patients with ocular MG.

5.3.4.3 Single fiber electromyography:

d. Single fiber electromyography (SFEMG) records action potentials from single muscle fibers in a motor unit.

e. A "jitter" phenomenon usually is noted and it represents variability of the time interval between the action potentials of 2 single muscle fibers in the same motor unit.

f. This test is highly sensitive in MG, technically demanding and operator dependent. It has a lower specificity, and it can give positive results in other neuromuscular disorders.

Appendix1: Figure 2- a flow chart for the Neurophysiological diagnosis of Myasthenia is

5.3.4.4 Imaging Studies:

a. MRI or CT scan of the brain and orbit is essential in ocular MG to rule out mass lesions compressing cranial nerves.

b. MRI or CT of the mediastinum (thin sections) is indicated to rule out a thymoma or thymic enlargement

5.4 Diagnosis Ascertainment

As a general rule, a firm diagnosis of MG is based upon a characteristic history and physical examination and more:

5.4.1 Presence of serum anti-AChR or anti-MuSK antibodies

5.4.2 2-3 Hertz repetitive nerve stimulation with decrement (single nerve fiber electromyography (SFEMG) with jitter studies may be needed), although, with a typical clinical picture and positive antibodies, electrophysiology is not required for diagnosis. It should be noted that EMG and sometimes also SFEMG show no clear abnormalities in MuSK-MG patients.

5.4.3 Nevertheless, SFEMG is sometimes helpful in monitoring response to treatment. Therefore, if available, electrophysiology studies should be performed as they are generally helpful and a good support for diagnosis and possibly for response to treatment.

If all the above investigations are negative:

5.4.4 Very clear positive clinical response to treatment with pyridostigmine, corticosteroids or other immunosuppressive treatment and/or plasma exchange or IVIg.

5.4.5 Unequivocally positive Tensilon or neostigmine test (with precautions against respiratory/cardiac complications), although some false positivity may occur.

See Appendix1: (C) Figure 3- a proposed diagnostic algorithm for MG

5.5 Classification:

5.5.1 Required data for clinical and laboratory classification

a. Basic clinical description of MG
b. Electrophysiological features
c. Antibody status
d. Treatment, response to it, and complications
e. Thymectomy and surgery-related complications; thymic histology

5.5.2 Clinical assessment and classification

a. Ocular vs. Generalized MG
b. Early vs. Late onset MG
c. AChR-MG vs. MuSK-MG vs. SNMG
d. MG associated to Thymoma Vs MG without Thymoma

5.6 Severity

5.6.1 Myasthenia Gravis Foundation of America (MGFA) clinical classification

The MGFA Clinical Classification divides MG into 5 main classes and several subclasses, as follows:

a. **Class I:** Involves any ocular muscle weakness, including weakness of eye closure. All other muscle groups are normal.
b. **Class II:** Involves mild weakness of muscles other than ocular muscles. Ocular muscle weakness of any severity may be present.
    i. **Class IIa:** Involves predominant weakness of the limb, axial muscles, or both. It may also involve the oropharyngeal muscles to a lesser extent.
    ii. **Class IIb:** Involves mostly oropharyngeal, respiratory muscles, or both. It can have the involvement of limb, axial muscles, or both to a lesser extent.
c. **Class III:** Involves muscles other than ocular muscles moderately. Ocular muscle weakness of any severity can be present.
    i. **Class IIIa:** involves the limb, axial muscles, or both predominantly. Oropharyngeal muscles can be involved to a lesser degree.

ii. **Class IIIb:** Involves oropharyngeal, respiratory muscles, or both predominantly. The limb, axial muscles, or both can have lesser or equal involvement.

d. **Class IV:** Involves severe weakness of affected muscles. Ocular muscle weakness of any severity can be present.

i. **Class IVa:** Involves limb, axial muscles, or both predominantly. Oropharyngeal muscles can be involved to a lesser degree.

ii. **Class IVb:** Involves oropharyngeal, respiratory muscles, or both predominantly. The limb, axial muscles, or both can have lesser or equal involvement. It also includes patients requiring feeding tubes without intubation.

e. **Class V:** Involves intubation with or without mechanical ventilation, except when employed during routine postoperative management.

5.6.2 Quantitative MG score for disease severity

The quantitative myasthenia gravis score (QMGS) is a 13-item scale used to quantify disease severity of MG.

The scale measures ocular, bulbar, respiratory, and limb function, grading each finding, and ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits).

See Appendix 2: (A) Table 1-The item scale used in QMGS.

5.6.3 Follow-up/evolution/course of disease

a. MGFA MG therapy status

b. MGFA Post intervention status

5.7 Therapeutic management:

5.7.1 Treatment Goals and preliminary definitions

While there is no known cure for myasthenia gravis (MG), there are several effective treatments. Spontaneous improvement and even remission, although uncommon, may occur without any specific therapy. However, as every case of MG is unique, a treatment plan should be designed according to the patient's needs. The followings should be considered:

a Treatment costs and availability.

b Clinical examination findings performed by a neurologist physician skilled in the evaluation of neuromuscular disease.

c The MGFA Clinical Classification, including remission, refers to the state of the patient at the time of evaluation.

5.7.2 Goals for the treatment of MG.

MGFA Task Force Post-Intervention Status (PIS) classification Minimal Manifestation Status (MMS) or better, with no more than grade 1 Common Terminology Criteria for Adverse Events (CTCAE) medication side effects. MMS: The patient has no symptoms or functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of remission have mild weakness.

CTCAE grade 1 medication side effects: asymptomatic or only mild symptoms; intervention not indicated.

5.8 Treatment Options

Treatment is categorized, in this guideline, for the following:

1. Symptomatic and immunosuppressive (IS) treatments
2. IV immunoglobulin (IVIg) and plasma exchange (PLEX)
3. Impending and manifest myasthenic crisis
4. Thymectomy
5. Juvenile MG (JMG)
6. MG with antibodies to muscle-specific tyrosine kinase (MuSK-MG)
7. MG in pregnancy
8. New medications

See appendix1: (D) figure 4-treatment options for myasthenia gravis.

5.8.1 Symptomatic and immunosuppressive (IS) treatments

a. Anti-acetylcholinesterase agents:

Mestinon® (pyridiostigmine bromide) allows acetylcholine to remain at the neuromuscular junction for a longer period, which in turn allows activation of more receptor sites, resulting in increased conductivity and muscle engagement. Mestinon® comes in two forms, Regular fast-acting 60 mg tablets (greatest effect usually occurs in 60

to 90 minutes and lasts for 3 to 4 hours) and extended long lasting slow-release 180 mg capsules known as Timespan® (which delivers pyridiostigmine bromide over a 12-hour period). Regular Mestinon is given PO in divided doses spaced to provide maximum relief when maximum strength is needed, i.e. adjusted dosages to the needs of the individual patient; dosage range, 60 to 1,500 mg/day. Whenever frequent doses are needed to control severe symptoms or nocturnal respiratory weakness, Mestinon Timespan® is usually given (typically in 1 to 3 tablet a day or as a bedtime dose so that the patient does not need to wake up every 3 or 4 hours to take a dose of regular Mestinon®).

b. Corticosteroids and immunosuppressant agents:

Corticosteroids, such as Prednisone or **an immunosuppressant agent** (including azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus), B-cells depleting agent-Anti CD20 (Rituximab) and complement inhibitors that block cleavage of C5 (Eculizumab) can be prescribed as a stand-alone medication or in combination.

These medications suppress body's production of antibodies that may be blocking or binding onto the acetylcholine receptors.

5.8.3 Recommendations for Symptomatic and immunosuppressive (IS) treatments

1. Pyridostigmine should be part of the initial treatment in most patients with MG. Pyridostigmine dose should be adjusted as needed based on symptoms. The ability to discontinue pyridostigmine can be an indicator that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or IS therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine.
2. A non-steroidal IS agent should be used alone when corticosteroids are contraindicated or refused. A non-steroidal IS agent should be used initially in conjunction with corticosteroids when the risk of steroid side effects is high based on medical comorbidities.

A nonsteroidal IS agent should be added to corticosteroids when:

a. Steroid side effects, deemed significant by the patient or the treating physician, develop
b. Response to an adequate trial of corticosteroids is inadequate; or

c. The corticosteroid dose cannot be reduced due to symptoms' relapse.

3. The following factors should be considered in selecting among non-steroidal IS agents that can be used in MG:
    a. There is widespread variation in practice with respect to choice of IS agent since there is little literature comparing them.
    b. Expert consensus and some RCT evidence support the use of azathioprine as a first line IS agent in MG.
    c. Evidence from RCTs supports the use of cyclosporine in MG, but potential serious adverse effects and drug interactions limit its use.
    d. Although available RCT evidence does not support the use of mycophenolate and tacrolimus in MG, both are widely used, and one or both are recommended in several national MG treatment guidelines.
    e. Although evidence from RCTs is lacking, oral Methotrexate (MTX) may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by RCT data.
    f. Rituximab (RTX) should be considered as an early therapeutic option in patients with MuSK-Ab+ MG who have an unsatisfactory response to initial immunotherapy. The efficacy of RTX in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents.
    g. Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG. The role of eculizumab in the treatment of MG is likely to evolve over time. It should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. Recommendations regarding immunization against meningococcal meningitis should be followed before treatment with eculizumab; as well as assessment of the duration of eculizumab therapy necessary to achieve and maintain treatment goals, its efficacy in other MG populations (MG with thymoma and seronegative MG), and in

other stages of disease (MG crises, exacerbations, and early therapy in nonrefractory AChR-Ab+ MG).

4. **Immune suppressants Agent dosage and duration of treatment:**
    a. Once patients achieve treatment goals, the corticosteroid dose should be gradually tapered. In many patients, continuing a low dose of corticosteroids long-term can help to maintain the treatment goal.
    b. For nonsteroidal IS agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the IS dose should be tapered slowly to the minimal effective amount. Dosage adjustments should be made no more frequently than every 3–6 months.
    c. Tapering of IS drugs is associated with risk of relapse, which may necessitate upward adjustments in dose. The risk of relapse is higher in patients who are symptomatic, or after rapid taper. d. It is usually necessary to maintain some immunosuppression for many years, sometimes for life.
5. Patients should be monitored for potential adverse effects and complications from IS drugs. Changing to an alternative IS agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.
6. For Ocular MG **:**
    a. Ophthalmoparesis or ptosis in ocular MG that is not responding to anticholinesterase agents should be treated with immunosuppressant agents if symptoms are functionally limiting or troublesome to the patient.
    b. Corticosteroids should be used as the initial IS agent in ocular MG. Steroid-sparing IS agents may be needed when corticosteroids alone are ineffective, contraindicated, or not tolerated.
    c. Data from a single small RCT suggest that low-dose corticosteroids may be effective for ocular MG and may avoid side effects associated with high-dose corticosteroids.

d. AChR-Ab+ patients with ocular MG who do not respond adequately to acetylcholinesterases and who either prefer not to take IS therapy or have contraindications to or are refractory to IS agents may be offered thymectomy

7. Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX): It is a pooled antibody, and a biological agent used to manage various autoimmune, infectious, and inflammatory states. Autoantibodies in the blood that target acetylcholine receptors are the key problem in myasthenia gravis and IVIg acts to destroy, neutralize these autoantibodies and to block the production of new ones. It is usually used as part of what is called a rapid induction therapy. This is a form of treatment meant to quickly suppress the immune system and is typically used in myasthenic crisis (the sudden and severe worsening of disease symptoms); before a patient undergoes surgery; as a temporary medication while a patient transitions to other therapies that suppress the immune system; or for those with severe MG who don't respond to other treatments.

A typical IVIG infusion is usually given slowly over a few hours, with multiple infusions given over a few days administered in a hospital setting. Results are often temporary, so repeated treatments are often required.

8. IgG Sub-cue Hizentra

A new, less invasive method of delivering immune globulins (IgG) is being reviewed for MG use. This method is known as IgG sub-cue, which means subcutaneous or "under the skin". In this method of IgG delivery, a series of 4-6 short needles are placed into the subcutaneous layer of skin across the abdomen. These needles are connected in a spider web fashion to the pump. A typical sub-cue infusion may only take from 1-3 hours and can be done at home.

9. Therapeutic Plasma Exchange

Therapeutic Plasma Exchange, or Plasmapheresis – Also known as Plasma exchange or PLEX. This is a filtration procedure whereby abnormal antibodies are removed from blood plasma. This procedure requires two intravenous (IV) lines or a port placed before undergoing PLEX. It is used in severe worsening of disease symptoms or to quickly

improve strength prior to surgery. Due to continuous production of autoantibodies, repeated PLEX treatments may be required.

9.1 Recommendations for Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX)

a. PLEX and IVIg are appropriately used as shortterm treatments in patients with MG with lifethreatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.
b. The choice between PLEX and IVIg depends on individual patient factors (e.g., PLEX cannot be used in patients with sepsis and IVIg cannot be used in renal failure) and on the availability of each.
c. IVIg and PLEX are probably equally effective in the treatment of severe generalized MG.
d. The efficacy of IVIg is less certain in milder MG or in ocular MG.
e. PLEX may be more effective than IVIg in MuSKMG.
f. The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom IS agents are relatively contraindicated.
   Impending and manifest myasthenic crisis.

10. Impending and manifest myasthenic crisis

Impending and manifest myasthenic crisis are emergent situations requiring aggressive management and supportive care. Although cholinergic crises are now rare, excessive ChEI cannot be completely excluded as a cause of clinical worsening. Also, ChEIs increase airway secretions, which may exacerbate breathing difficulties. PLEX and IVIg are the mainstay of management in myasthenic crisis.

a. Impending crisis requires hospital admission and close observation of respiratory and bulbar function, with the ability to transfer to an intensive care unit if it progresses to manifest crisis. Myasthenic crisis requires admission to an intensive

care or step-down unit to monitor for or manage respiratory failure and bulbar dysfunction.

b. PLEX and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction. Corticosteroids or other IS agents are often started at the same time to achieve a sustained clinical response. (Because corticosteroids may cause transient worsening of myasthenic weakness, it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids).
c. Although clinical trials suggest that IVIg and PLEX are equally effective in the treatment of impending or manifest myasthenic crisis, expert consensus suggests that PLEX is more effective and works more quickly. The choice between the 2 therapies depends on patient comorbidity (e.g., PLEX cannot be used in sepsis and IVIg is contraindicated in hypercoagulable states, renal failure, or hypersensitivity to immunoglobulin) and other factors, including availability. A greater risk of hemodynamic and venous access complications with PLEX should also be considered in the decision (many complications of PLEX are related to route of access and may be minimized by using peripheral rather than central venous access)

10.1 Thymectomy for MG

Surgical removal of the thymus gland is highly effective in MG patients. Effectiveness of this surgical procedure varies with each patient and It is removed in an effort to improve the weakness caused by autoantibody production, and to remove a thymoma (usually benign or in some cases malignant) that presents itself in only 10% of patients.

The neurological goals of a thymectomy are significant improvement in the patient's weakness, reduction in the medications being employed, and ideally a permanent remission (complete elimination of all weakness and off all medications). A thymectomy is usually not used to treat active disease but rather it is believed to improve long-term outcome. Results may not be seen for one to two years or more after the thymectomy.

10.2 Recommendations for Thymectomy in MG

a. In nonthymomatous, generalized MG patients with AChR-Ab, aged 18–50 years, thymectomy should be considered early in the disease to improve clinical outcomes and to minimize immunotherapy requirements and the need for hospitalizations for disease exacerbations
b. Thymectomy should be strongly considered in patients with AChR-Ab+ generalized MG if they fail to respond to an initial adequate trial of immunotherapy or have intolerable side effects from that therapy
c. Thymectomy for MG is an elective procedure and should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function.
d. The value of thymectomy in the treatment of prepubertal patients with MG is unclear, but thymectomy should be considered in children with generalized AChR antibody–positive MG:
e. . If the response to pyridostigmine and IS therapy is unsatisfactory; or
f. . In order to avoid potential complications of IS therapy.
g. For children diagnosed with seronegative generalized MG, the possibility of a congenital myasthenic syndrome or other neuromuscular condition should be entertained, and evaluation at a center specializing in neuromuscular diseases is of value prior to thymectomy with rare exceptions, all patients with MG with thymoma should undergo surgery to remove the tumor. Removal of the thymoma is performed to rid the patient of the tumor and may not produce improvement in MG.
h. All thymus tissue should be removed along with the tumor. Further treatment of thymoma will be dictated by histological classification and degree of surgical excision. Incompletely resected thymomas should be managed after surgery with an interdisciplinary treatment approach (radiotherapy, chemotherapy).
i. In elderly or multimorbid patients with thymoma, palliative radiation therapy can be considered in the appropriate clinical setting. Small thymomas may be followed without treatment unless they are enlarging or become symptomatic

j. Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches.

k. Thymectomy may be considered in patients with generalized MG without detectable AChR-Ab if they fail to respond adequately to immunosuppressive therapy or to avoid/ minimize intolerable adverse effects from IS therapy.

l. Current evidence does not support an indication for thymectomy in patients with MuSK, low-density lipoprotein receptor–related protein 4, or agrin antibodies.

10.3 Recommendations for Treatment of Juvenile MG

a. Children with acquired autoimmune ocular MG are more likely than adults to go into spontaneous remission. Thus, young children with only ocular symptoms of MG can be treated initially with pyridostigmine.

   Immunotherapy can be initiated if goals of therapy are not met.

b. Children are at particular risk of steroid side effects, including growth failure, poor bone mineralization, and susceptibility to infection, due in part to a delay in live vaccinations. Long-term treatment with corticosteroids should use the lowest effective dose to minimize side effects.

c. Maintenance PLEX or IVIg are alternatives to IS drugs in JMG.

10.4 Recommendations for Treatment of MG with MuSK antibodies.

1. Many patients with MuSK-MG respond poorly to ChEIs, and conventional pyridostigmine doses frequently induce side effects.
2. Patients with MuSK-MG appear to respond well to corticosteroids and to many steroid-sparing IS agents. They tend to remain dependent on prednisone despite concomitant treatment with steroid sparing agents.
3. MuSK-MG responds well to PLEX, while IVIg seems to be less effective.
4. Rituximab should be considered as an early therapeutic option in patients with MuSK-MG who have an unsatisfactory response to initial immunotherapy

11. Treatment of MG in pregnancy:

a. Planning for pregnancy should be instituted well in advance to allow time for optimization of myasthenic clinical status and to minimize risks to the fetus.

b. Multidisciplinary communication among relevant specialists should occur throughout pregnancy, during delivery, and in the postpartum period.

c. Provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that they will remain stable throughout pregnancy. If worsening occurs, it may be more likely during the first few months after delivery.

d. Oral pyridostigmine is the first-line treatment during pregnancy. IV ChEIs may produce uterine contractions and should not be used during pregnancy.

e. Thymectomy should be postponed until after pregnancy as benefit is unlikely to occur during pregnancy.

f. Chest CT without contrast can be performed safely during pregnancy, although the risks of radiation to the fetus need to be carefully considered. Unless there is a compelling indication, postponement of diagnostic CT until after delivery is preferable.

g. Prednisone is the IS agent of choice during pregnancy.

h. Current information indicates that azathioprine and cyclosporine are relatively safe in expectant mothers who are not satisfactorily controlled with or cannot tolerate corticosteroids. Current evidence indicates that mycophenolate mofetil and methotrexate increase the risk of teratogenicity and are contraindicated during pregnancy. (These agents previously carried Food and Drug Administration [FDA] Category C (cyclosporine), D (azathioprine and mycophenolate mofetil), and X (methotrexate) ratings. The FDA has recently discontinued this rating system, and replaced it with a summary of the risks of using a drug during pregnancy and breastfeeding, along with supporting data and “relevant information to help health care providers make prescribing and counseling decisions”).

i. Although this statement achieved consensus, there was a strong minority opinion against the use of azathioprine in pregnancy. Azathioprine is the non-steroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the United

States. This difference is based on a small number of animal studies and case reports. 9. PLEX or IVIg are useful when a prompt, although temporary, response is required during pregnancy. Careful consideration of both maternal and fetal issues, weighing the risks of these treatments against the requirement for use during pregnancy and their potential benefits, is required.

j. Spontaneous vaginal delivery should be the objective and is actively encouraged.
k. Magnesium sulfate is not recommended for management of eclampsia in MG because of its neuromuscular blocking effects; barbiturates or phenytoin usually provide adequate treatment.
l. All babies born to myasthenic mothers should be examined for evidence of transient myasthenic weakness, even if the mother's myasthenia is well-controlled, and should have rapid access to neonatal critical care support.

12. New Medications: see Appendix 2Table -2)

The following are new FDA-approved medications for generalized myasthenia gravis:

12.1 Neonatal Fc receptor (FcRn) blockers

a. The U.S. Food and Drug Administration (FDA) have approved argenx's VYVGART® (efgartigimod alfa-fcab) for the treatment of generalized myasthenia gravis (GMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
b. These patients represent approximately 85% of the total gMG population. VYVGART is a prescription medication and the first FDA-approved treatment that uses a fragment of an IgG antibody to treat adults with anti-AChR antibody positive generalized myasthenia Gravis. It is given in treatment cycles with a break between each cycle.
c. A treatment cycle consists of a 1-hour infusion each week for 4 weeks (4 infusions total). The treatment is specifically designed to attach to and block the neonatal Fc receptor (FcRn), resulting in the reduction of IgG antibodies, including the harmful AChR antibodies that cause gMG symptoms. Receptors called "FcRn" extend the life of IgG antibodies. In gMG, this allows harmful AChR antibodies to continue causing gMG symptoms. But IgG antibodies, including harmful AChR antibodies, that cannot attach to an FcRn are removed by the body. When harmful AChR

antibodies that cause GMG symptoms are removed, they can no longer disrupt nerve-muscle communication.

12.2 C5 Protein Inhibitors:

a. AstraZeneca, and its Alexion rare disease group, announced that the United States Food & Drug Administration (FDA) has officially approved the Ultomiris® (ravulizumab-cwvz) treatment for adult patients with generalized myasthenia gravis (GMG) who are anti-acetylcholine receptor (AChR) antibody-positive, which represents 80% of people living with the disease.

b. The FDA action marks the first and only approval for a long-acting C5 complement inhibitor for the treatment of GMG. According to Alexion, the medication works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system. When activated in an uncontrolled manner, the complement cascade over-responds, leading the body to attack its own healthy cells.

c. Ultomiris is administered intravenously every eight weeks in adult patients, following a loading dose. Ultomiris showed early effect and lasting improvement in activities of daily living and has potential to reduce treatment burden with dosing every 8 weeks.

12.3 Rozanolixizumab-noli (brand name Rystiggo®). Approved in 2023, this is the first FDA-approved treatment for both anti-AChR and anti-MuSK antibody-positive myasthenia gravis. It targets a receptor that can stop harmful antibodies from being broken down by the cells' natural waste clearance system (blocks FcRn). It's administered by subcutaneous (under the skin) infusion once a week for six weeks.

12.4 Zilucoplan (brand name ZILBRYSQ®). This was also approved in 2023, and it's the first myasthenia gravis therapy for self-administration by a daily injection. It works using a targeted mechanism to inhibit damage to the neuromuscular junction by complement inhibition.

See Appendix 1 (E) figure 5-Treatment approach to Myasthenia Gravis patients

12.3 Cautionary Drugs:

Certain medications may cause worsening of MG symptoms and should be avoided or use with caution in MG patients. A list of cautionary drugs (**see Appendix 2: Table 3)**

13. Responsibilities:

13.1 Head Of Neurology Department Shall:

13.1.1 Ensure all doctors in the department are aware about this guideline.

13.2 Neurology Doctors Shall:

13.2.1 be aware and adhere to this guideline.

Chapter 4

14. Document History and Version Control:

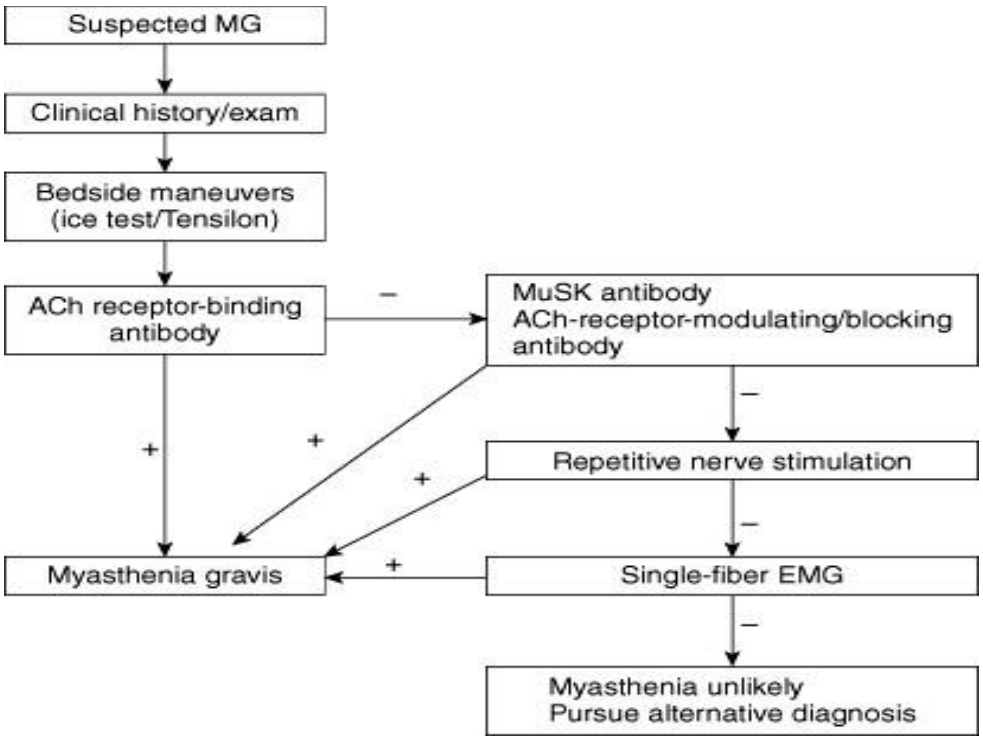
Version	Description	Author Names	Review Date
1	Initial Release	Dr. Ahmed Sameer	2025
2	Version two	Dr. Ahmed Sameer	2027

15. References:

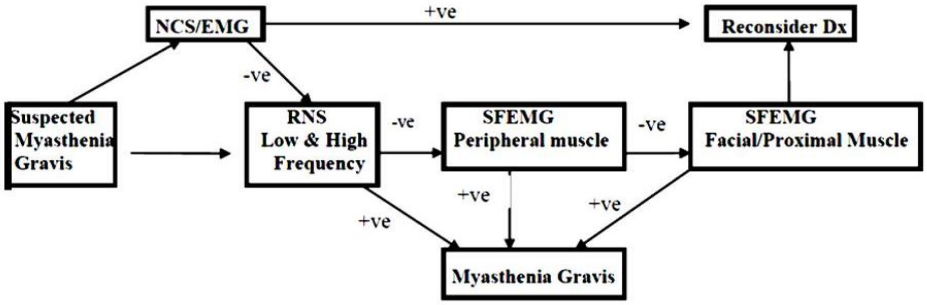
1. Benatar M. A systematic review of diagnostic studies in myasthenia gravis, Neuromuscul. Disord. 2006; 16: 459–467.
2. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology.* 2000 Jul 12; 55(1):16-23.
3. Myology. 2nd Ed. New York: McGraw Hill. Engel AG. Myasthenic syndromes. In: Engel AG, Franzini Armstrong C, editors. 19941,798-835
4. Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle Nerve Oh SJ, Kim DE, Kuruoglu R, et al. 1992 15:720
5. A reappraisal of diagnostic tests for myasthenia gravis in a large Asian cohort. J Neurol Sci. Lo YL, Najjar RP, Teo KY, Tow SL, Loo JL, Milea D. 2017. 376:153-158
6. The epidemiology of neuromuscular disorders: a comprehensive overview of the literature. J Neuromuscul Dis. Deenen JC, Horlings CG, Verschuuren JJ, et al.2015. 2(1):73–85
7. Misdiagnosis of Myasthenia Gravis and Subsequent Clinical Implication: A case report and review of literature. Sultan Qaboos Univ Med J. Al-Asmi A, Nandhagopal R, Jacob PC, Gujjar A. 2012 12(1):103-108.
8. Electrophysiological and immunological study in myasthenia gravis: diagnostic sensitivity and correlation. Clin Neurophysiol. Witoonpanich R, Dejthevaporn C, Sriphrapradang A, Pulkes T 2011 122:1873–7
9. Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. J Neurol Neurosurg Psychiatry. Vincent A, Newsom-Davis J. 198548:1246 –1252.
10. An ice test for the diagnosis of myasthenia gravis, Ophthalmology. Golnik KC, Pena R, Lee AG, Eggenberger ER, 1999, 106: 1282–1286.
11. International Consensus Guidance for Management of Myasthenia Gravis.2020 Update.
12. Neurology, the journal of the American Academy of Neurology. Pushpa Narayana swami, et.al. 2021 96:114-122.

16. Annexes:

16.1 Appendix 1: (A) Figure 1: Diagnostic Approach to MG:

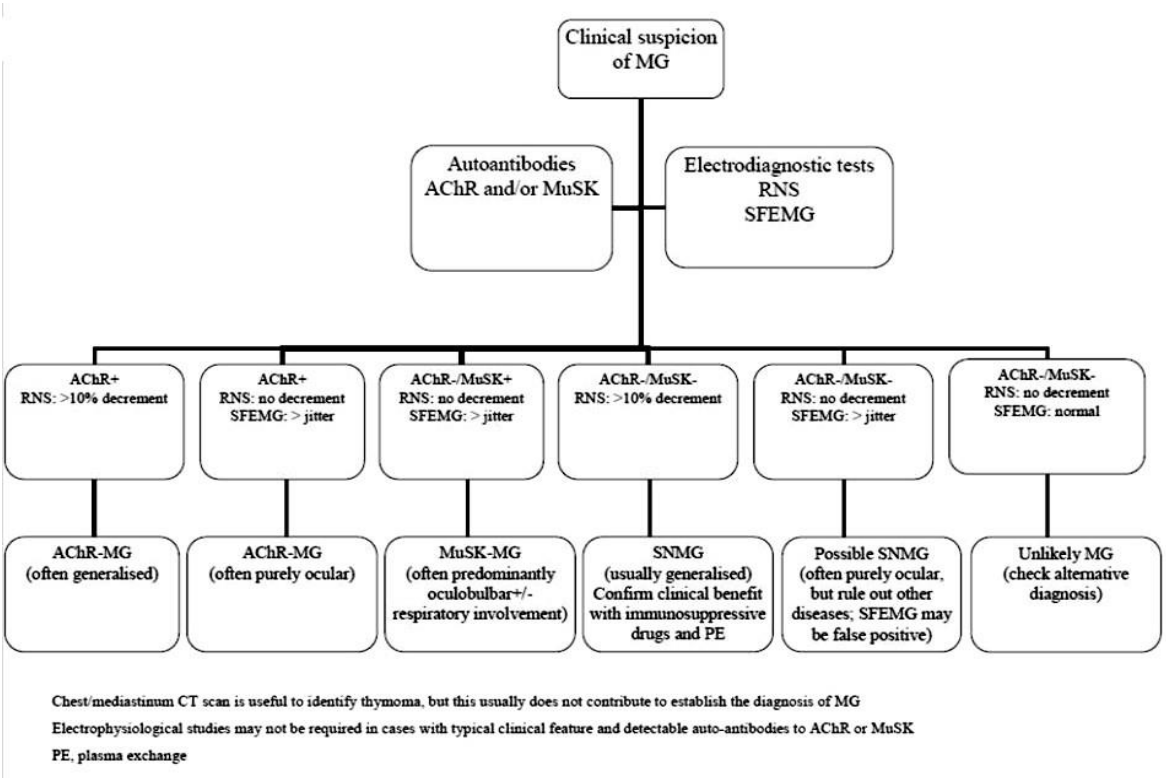


16.1 Appendix (B) Figure 2: A flow chart for the Neurophysiological diagnosis of Myasthenia Gravis



NCS: Nerve conduction study, EMG: Electromyography, SFEMG: Single fiber EMG
RNS: Repetitive nerve stimulation
-ve: Negative result, +ve: Positive results

16.1 Appendix (C) Figure 3: Proposed Diagnostic Algorithm for MG

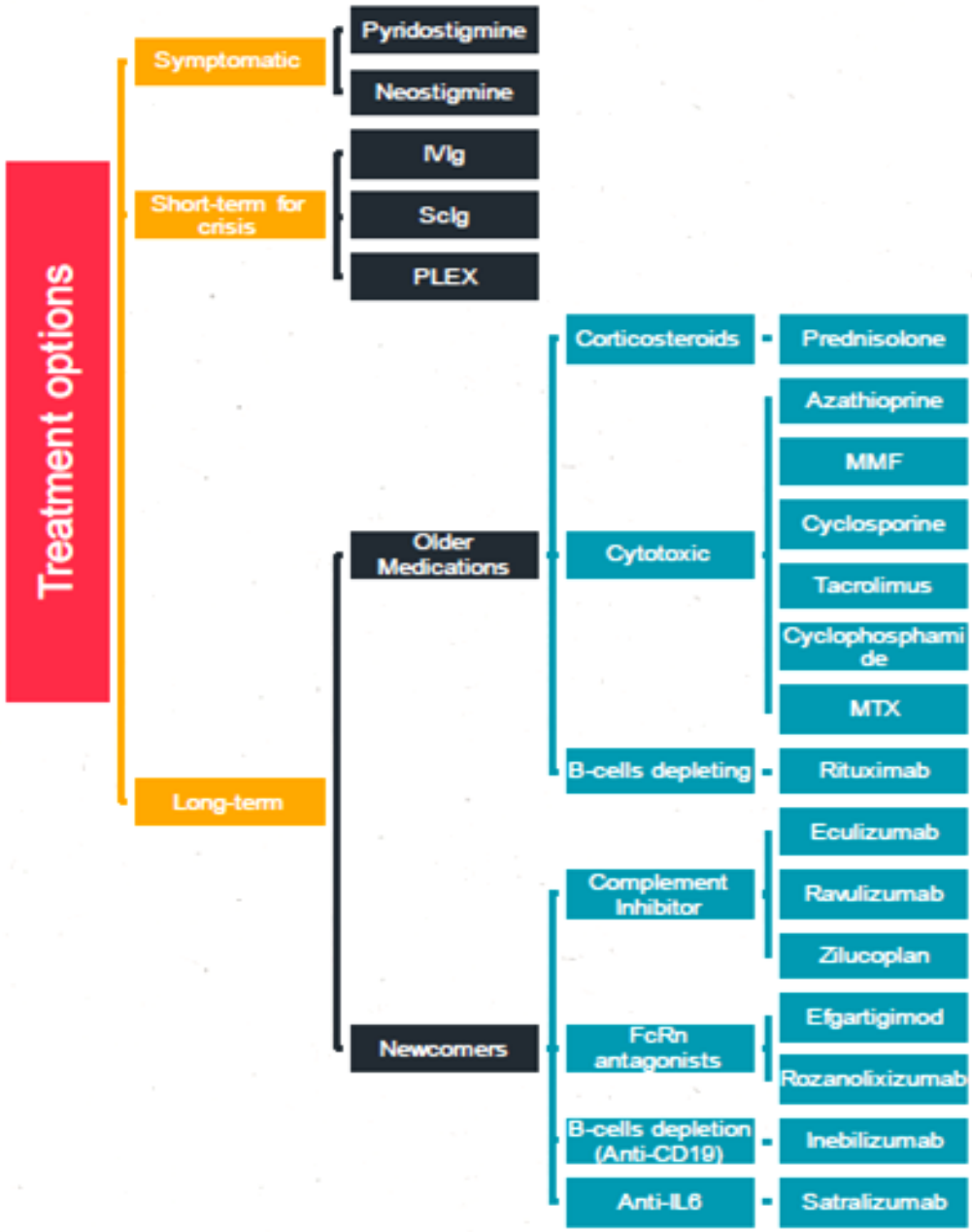


Chest/mediastinum CT scan is useful to identify thymoma, but this usually does not contribute to establish the diagnosis of MG

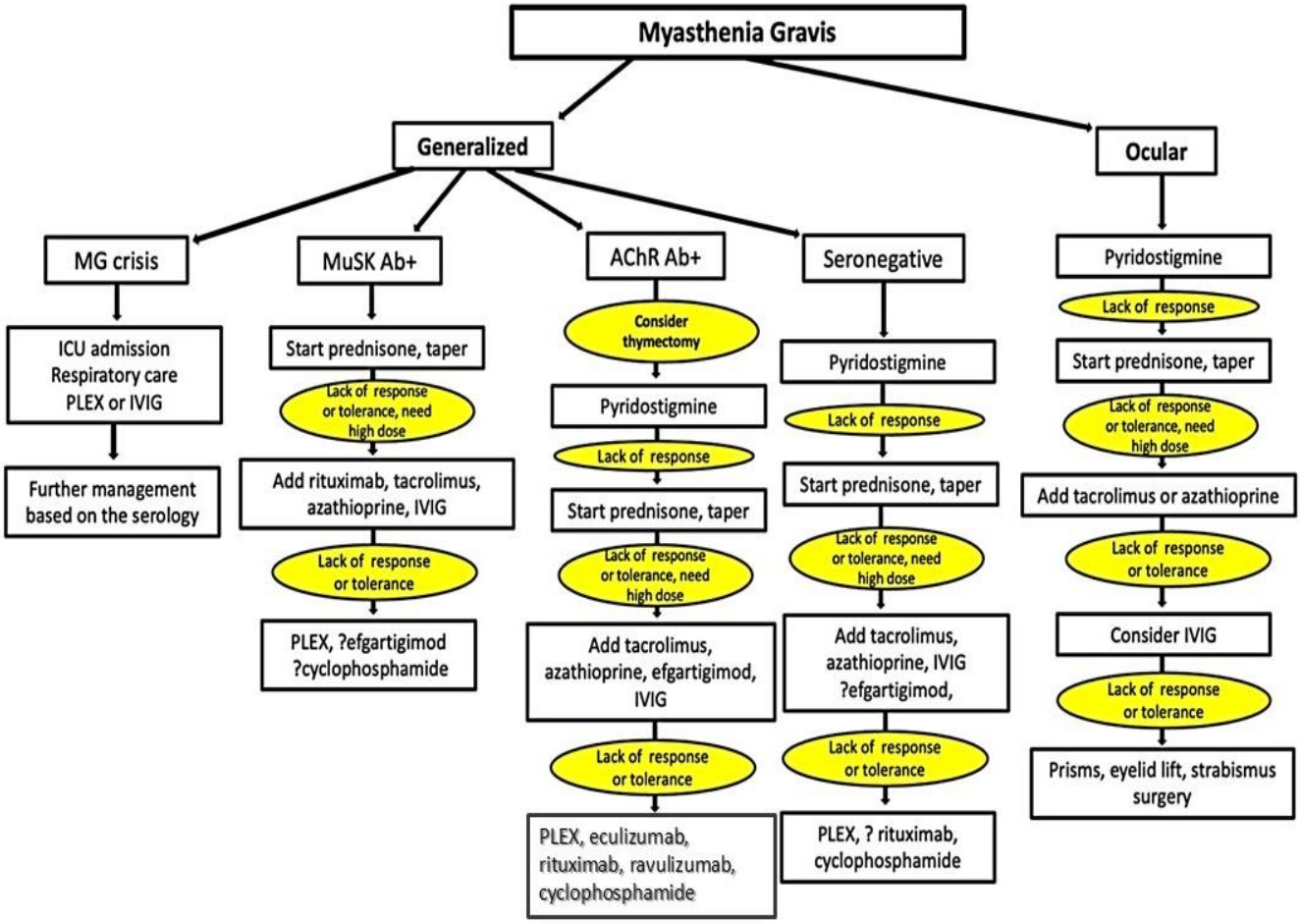
Electrophysiological studies may not be required in cases with typical clinical feature and detectable auto-antibodies to AChR or MuSK

PE, plasma exchange

16.1 Appendix (D) Figure 4: Treatment options for Myasthenia Gravis



16.1 Appendix (E) Figure 5: Treatment Approach to Myasthenia Gravis patients



16.2 Appendix2:

16.2 (A) Table 1: The quantitative myasthenia gravis score (QMGS):

Test Item Grade	0	1	2	3
Double vision on lateral gaze right or left (circle one)	61 sec	11–60 sec	1–10 sec	Spontaneous
Ptosis (upward gaze)	61 sec	11–60 sec	1–10 sec	Spontaneous
Facial muscles	Normal lid	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz water (½ cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech following counting aloud from 1 to 50 (onset of dysarthria)	None at #50	Dysarthria at #30–49	Dysarthria at #10–29	Dysarthria at #9
Right arm outstretched (90° sitting)	240 sec	90–239 sec	10–89 sec	0–9 sec
Left arm outstretched (90° sitting)	240 sec	90–239 sec	10–89 sec	0–9 sec
Vital capacity (% predicted)	≥80%	65–79%	50–64%	<50%
Right-hand grip (KgW) Male Female	 ≥45 ≥30	 15–44 10–29	 5–14 5–9	 0–4 0–4
Left-hand grip (KgW) Male Female	 ≥35 ≥25	 15–34 10–24	 5–14 5–9	 0–4 0–4
Head, lifted (45° supine)	120 sec	30–119 sec	1–29 sec	0 sec
Right leg outstretched (45° supine)	100 sec	31–99 sec	1–30 sec	0 sec
Left leg outstretched (45° supine)	100 sec	31–99 sec	1–30 sec	0 sec
TOTAL QMG SCORE				

(From Barohn RJ et al. Reliability testing of the quantitative myasthenia gravis score. Ann NY Acad Sci 1998;841:769.)

16.2 (B) Table 2: New approved medications for Myasthenia Gravis patients:

Treatment	Mechanism	FDA	Indication	Route	Dose
Eculizumab (Soliris)	Blocks terminal complement cascade	2017	AChR+ gMG	IV	Initial loading dose of 900 mg, followed by maintenance doses of 1200 mg every 2 weeks
Efgartigimod (Vyvgart)	Blocks FcRn receptor	2021	AChR+ gMG	IV	10 mg/kg once weekly for 4 weeks, followed by a variable interval based on response and tolerability
Ravulizumab	Blocks terminal complement cascade	2022	AChR+ gMG	IV	Single loading dose followed by maintenance doses administered every 8 weeks
Rozanolixizumab-noli (Rystiggo)	Blocks FcRn receptor	2023	AChR+ or MuSK+ gMG	SC	700 mg weekly for 6 weeks, followed by 700 mg every 4 weeks thereafter
Zilucoplan (ZILBRYSQ)	Complement inhibitor	2023	AChR+ gMG	SC	600 mg once weekly for 4 weeks, followed by 300 mg once weekly thereafter

16.2 (C) Table 3: Drugs to be avoided or use in caution for patients with MG:

Drug	Comment
Aminoglycoside antibiotics (e.g., gentamycin, neomycin, and tobramycin)	Used for gram-negative bacterial infections. May worsen MG. Use cautiously if no alternative treatment available.
Beta-blockers	Commonly prescribed for hypertension, heart disease, and migraine but potentially dangerous in MG. May worsen MG. Use cautiously.
Botulinum toxin	Presynaptic neuromuscular junction blocker. Avoid use.
Chloroquine and hydroxychloroquine	Used to treat/prevent malaria and for certain autoimmune diseases. May precipitate de novo MG or worsen preexisting MG. Use only if necessary and observe for worsening.
Corticosteroids	A standard treatment for MG but may cause transient worsening within the first 2 weeks. Monitor carefully for this possibility.
Desferrioxamine (deferoxamine)	Chelating agent used for hemochromatosis. May worsen MG.
D-Penicillamine	Used for Wilson disease and rarely for rheumatoid arthritis. Strongly associated with causing MG. Avoid use.
Fluoroquinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin)	Commonly prescribed broad-spectrum antibiotics that are associated with worsening MG. The US FDA has designated a "black-box" warning for these agents in MG. Use cautiously, if at all.
Immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab, atezolizumab, and nivolumab)	Used for certain cancers. Can precipitate de novo MG or worsen preexisting MG. Use with caution as determined by oncologic status.
Iodinated radiologic contrast agents	Older reports document increased MG weakness, but modern contrast agents appear safer. Use cautiously and observe for worsening.
Macrolide antibiotics (e.g., erythromycin, azithromycin, and clarithromycin)	Commonly prescribed antibiotics for gram-positive bacterial infections. May worsen MG. Use cautiously, if at all.
Magnesium	Potentially dangerous if given intravenously, i.e., for eclampsia during late pregnancy or for hypomagnesemia. Use only if absolutely necessary and observe for worsening.
Procainamide	Used for irregular heart rhythm. May worsen MG. Use with caution.
Quinine	Occasionally used for leg cramps. Use prohibited except in malaria in the United States.
Statins(e.g., atorvastatin, pravastatin, rosuvastatin, and simvastatin)	Used to reduce serum cholesterol. May rarely worsen or precipitate MG. Evaluate closely for worsening MG when statin treatment is commenced.
Telethromycin	Antibiotic for community-acquired pneumonia. Associated with hepatoxicity and risk of prolonged QTc interval. Causes severe, often fatal worsening in MG. Had been given a "black-box" warning by the US FDA contraindicating use in MG. Drug withdrawn from most markets internationally. Should not be used in MG.
Live-attenuated vaccines (measles, mumps, rubella, varicella zoster, intranasal influenza, oral polio, adenovirus type 4 and 7, Zostavax (herpes zoster), rotavirus, oral typhoid, smallpox, and yellow fever)	Do not affect MG but are contraindicated in patients on immunosuppressive treatments because of the risk for adverse reactions due to uninhibited growth of the attenuated live virus or bacteria.

Abbreviation: MG = myasthenia gravis.
[a] Many drugs are associated with worsening of MG. However, reported associations do not necessarily mean these medications should never be prescribed in MG. Reports are often rare or represent a coincidental association. Clinical judgment and the risk-to-benefit ratio of the drug should be considered when it is deemed important for a patient's treatment. Listed above are medications that have the strongest evidence for worsening MG.