



Myasthenia Gravis: Clinical Guidelines

Introduction

There have been a number of publications on guidelines on MG diagnosis and treatment, and there are slightly different approaches and practices according to the authors' experience and target audience. **Our guidelines are directed to European clinicians with little experience on MG (GPs, other clinicians, and neurologists) working in different countries and conditions and under different health policies.**

The first aim of these recommendations is to help improve clinical practice in general, from symptoms to diagnosis, including diagnostic criteria, classification, differential diagnoses, and associated conditions.

The second aim is to advice on general management and treatments from first-line medications to immunosuppression and immunomodulation, to provide guidance on how to monitor MG patients and how to recognize and prevent exacerbations or crises, and also to list conditions and medications that can interfere with MG. In addition, these guidelines should help towards recognizing clinical stability while patients are still on medication and how to plan a very slow reduction of the medication and prevent relapses that may occur even in patients in MG remission.

As a final point, we want to stress the importance of having good and easy communication routes between patient and GP and specialist. Communication via letters, FAX, phone calls, and emails is crucial in the diagnosis and effective treatment of MG patients, and helps build mutual confidence.

These recommendations were prepared in the context of the WP5 of the EuroMyasthenia project and took into account comments and suggestions from D Hilton-Jones in Oxford and some of our partners (A. Melms, J. Verschuuren, Apostololski, M. Farrugia, A. Kostera-Pruszczyk, T. Chantall, F. Deymeer, I. Hart, N. E. Gillus, and M. Carvalho)

1. Myasthenia Gravis diagnosis

This section includes:

1.1 Background

1.2 Rationale

1.3 Diagnosis, classification and assessment

1.4 Diagnosis flowchart for MG

1.5 MGFA clinical classification.

1.1 Background

Myasthenia Gravis (MG) is a neuromuscular transmission disorder characterized by fluctuating weakness and fatigability of voluntary muscles (ocular, bulbar, limbs, neck and respiratory) without loss of reflexes or impairment of sensation or other neurologic function.

The neuromuscular transmission defect is usually demonstrated by pharmacological and electrophysiological tests.

MG is an autoimmune disorder and is usually (80% of 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.

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.

Cholinesterase inhibitors 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.

1.2 Rationale

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.

Standardisation 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, and evaluation and measuring of its clinical and functional features either at diagnosis or after treatment.

The standardization of clinical data helps also in the development and improvement of different lines of investigation: clinical, epidemiological and laboratory.

1.3 Diagnosis, classification and assessment

1.3.1 Diagnostic criteria (inclusion)

A. Characteristic signs and symptoms

- 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.
- Increased weakness during exercise and repetitive muscle use with at least partially restored strength after periods of rest.

- Clear improvement in strength following administration of a cholinesterase inhibitor (edrophonium or neostigmine).
- Positive response to immunosuppressive treatment.
- Dramatic improvement following plasma exchange or IVIg.

B. Decremental response of compound muscle action potential upon repetitive stimulation of a peripheral nerve (RSN): in MG, repetitive stimulation at a rate of 2-3 Hz per second shows a characteristic decremental (>10%) response which is reversed by edrophonium (Tensilon) or neostigmine (although this is not required for routine assessment). Single-fiber studies show increased jitter (see annexe on electrodiagnostic tests).

C. Antibodies to AChR or to MuSK

1.3.2 Exclusion/differential diagnosis

- Congenital myasthenic syndrome, myopathies (e.g. oculopharyngeal muscular dystrophy, mitochondrial progressive external ophthalmoplegia), steroid and inflammatory myopathies, motor neuron disease
- Eaton-Lambert syndrome
- Multiple sclerosis (weakness with chronic fatigue or subacute/acute brainstem or spinal cord motor involvement)
- Variants of Guillain-Barré syndrome (e.g., Miller-Fisher syndrome)
- Organophosphate toxicity, botulism, black widow spider venom
- Stroke
- Hypokalemia; hypophosphatemia

1.3.3 Associations (MG is often associated with)

- Thyroid abnormalities
- Other autoimmune diseases

- Thymoma

1.3.4 Ascertainment

As a general rule, a firm diagnosis is based upon a characteristic history and physical examination *plus:*

- Presence of serum anti-AChR or anti-MuSK antibodies
- 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. 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:

- Very clear positive response to immunosuppressive treatment and/or plasma exchange or IVIg
- Unequivocally positive Tensilon or neostigmine test (with precautions against respiratory/cardiac complications), although some false positivity may occur

1.3.5 Classification

Required data for clinical and laboratory classification

- Demographic data
- Basic clinical description of MG
- Electrophysiological features
- Antibody status
- Treatment, response to it, and complications

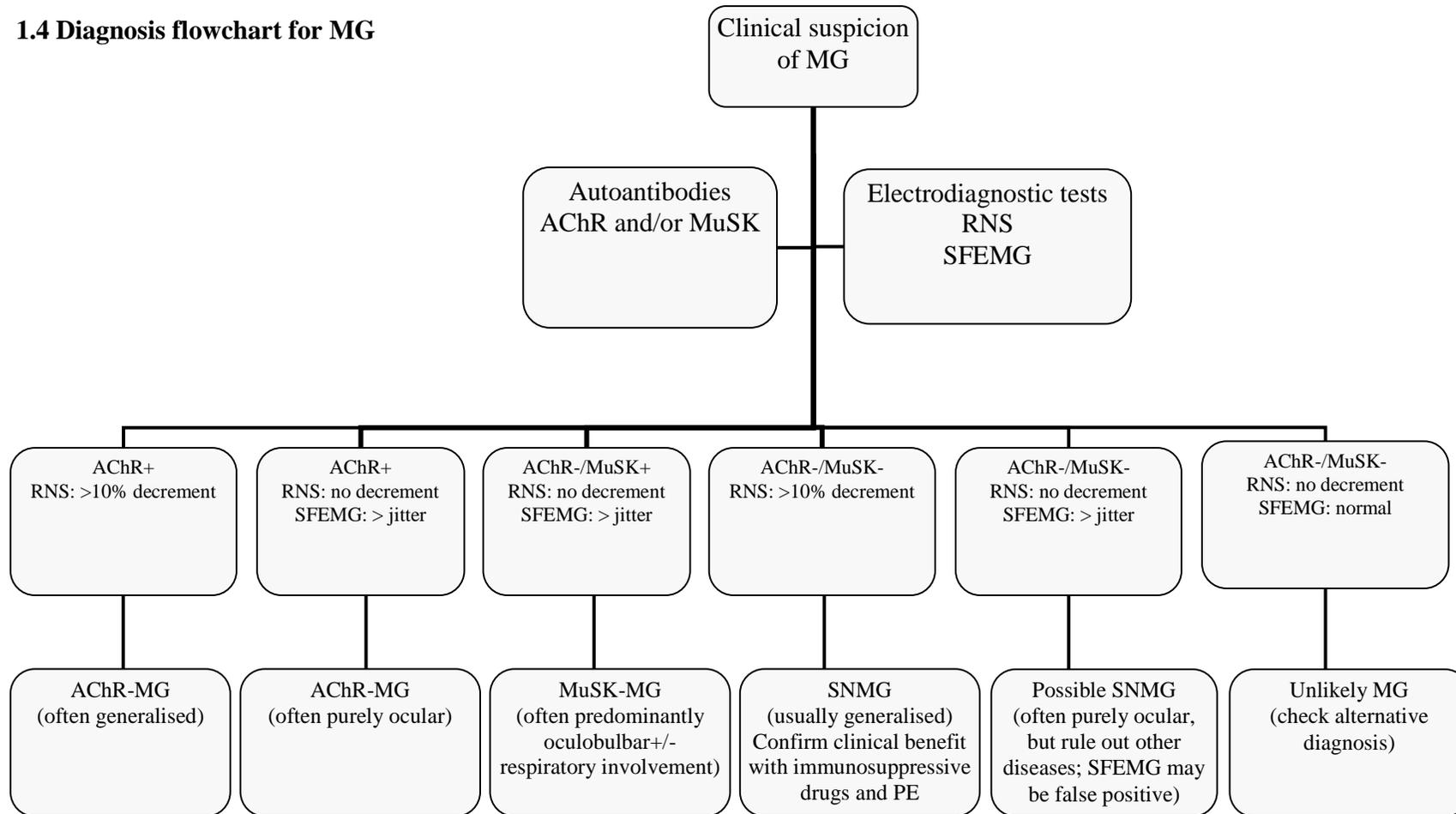
- Thymectomy and surgery-related complications; thymic histology

- Clinical assessment and classification
 - Ocular vs. generalised MG
 - Early vs. late onset MG
 - AChR-MG vs. MuSK-MG vs. SNMG
 - MG associated to thymoma

- Severity
 - MGFA clinical classification
 - Quantitative MG score for disease severity

- Follow-up/evolution/course of disease
 - MGFA MG therapy status
 - MGFA Postintervention status

1.4 Diagnosis flowchart 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

1.5 MGFA clinical classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. Strength of all the other muscles is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

2. Myasthenia Gravis monitoring and treatment

This section includes:

2.1 Recommendations on the most commonly used pharmacological agents and thymectomy

2.2 Advice on general monitoring of MG and of side effects of medication, and on how to manage disease exacerbation and remission

2.3 Treatment flowchart

2.4 Table/summary of the most commonly used treatments (their indications, advantages, adverse effects, disease parameters to be monitored, and adult dosages)

2.5 Drugs and toxins that adversely affect myasthenia gravis

2.6 Recommended literature for more detailed and complete information.

2.1 Medicaments, surgical treatment, and other therapeutic measures

Pyridostigmine (Mestinon), an anti-cholinesterase (AChE) drug, is the usual first-line treatment for MG. However, the treatment is mainly symptomatic. Therefore, patients on this medication alone should be evaluated soon after starting it to check their response and possible need for steroid and or other immunosuppressive or immunomodulatory therapy.

Steroid and/or immunosuppressive therapy should be considered in all patients with progressive and moderate or severe disease which does not respond adequately to pyridostigmine. Prednisolone is usually the first to use, because it has a relatively rapid onset of benefit (measured over weeks to a few months). If high doses are needed in the long term, side-effects are problematic and a steroid-sparing agent should be introduced, typically simultaneously with the prednisolone to allow a subsequent decrease in steroids to the lowest dose. Azathioprine is the most commonly used steroid-

sparing immunosuppressant, but has a long latency (as long as 12-18 months) before benefit begins and maximal effect is achieved. Other immunosuppressants probably work more rapidly, but still with a latency of not less than 3-4 months.

If the patient is intolerant of, or unresponsive to, azathioprine, and the required dose of prednisolone remains unacceptably high, then alternatives include methotrexate, mycophenolate mofetil (MMF), cyclosporin, tacrolimus, and cyclophosphamide. However, there is limited information concerning the balance between efficacy and safety for these agents and no entirely satisfactory clinical trials. Recently, rituximab has also been reported to be beneficial.

Plasma exchange (PE) and intravenous human immunoglobulin (IvIg) are used as a short-term treatment in MG patients with life-threatening signs such as respiratory insufficiency or dysphagia, in preparation for surgery, and when a very rapid response to treatment is needed. The choice between PE and IvIg depends on the patient (e.g. PE cannot be used in patients with sepsis) and on the availability and price of these treatments. Chronic use of IvIg may be helpful in patients with severe MG that do not respond to steroids and/or immunosuppressive drugs even at maximal doses. All the drugs should be used at the lowest dose possible; potential adverse effects and complications of any treatment should be known, monitored, prevented, and treated.

A Table (Section 2.4) summarises the most common non-surgical treatments in MG and includes indications, adult dosages (starting, maximal, and maintenance doses), as well as their side effects and how to prevent or monitor them.

Thymectomy should be done in all patients with thymoma. AChR-antibody positive early-onset patients with generalized MG, especially with insufficient response to pyridostigmine, should be considered for thymectomy, ideally in the first year upon diagnosis. Extended transsternal thymectomy is the operation of choice in all patients with thymoma. In MG patients without thymoma, both the extended transsternal surgery and transcervical (with direct visualization of thymus) thymectomy have been used. Although the latter appears to be cosmetically preferred, there is no evidence to prove equal efficacy of the transcervical to the open transsternal approach. Any type of thymectomy should be performed only by an experienced team (surgeon/anesthetist). The

results of the ongoing international thymectomy trial may provide clear evidence of the benefits of thymectomy in AChR-antibody-positive generalised MG without thymoma, and the recommendations will be updated accordingly.

2.2 Advice on general monitoring of MG and of side effects of medication, and on managing disease exacerbation and remission

Non-pharmacological measures to treat and monitor the disease are very important. Equally important are the regular visits of MG patients to their doctor. All patients with MG require regular long-term follow-up, primarily by their GP and also by a neurologist (probably less frequently).

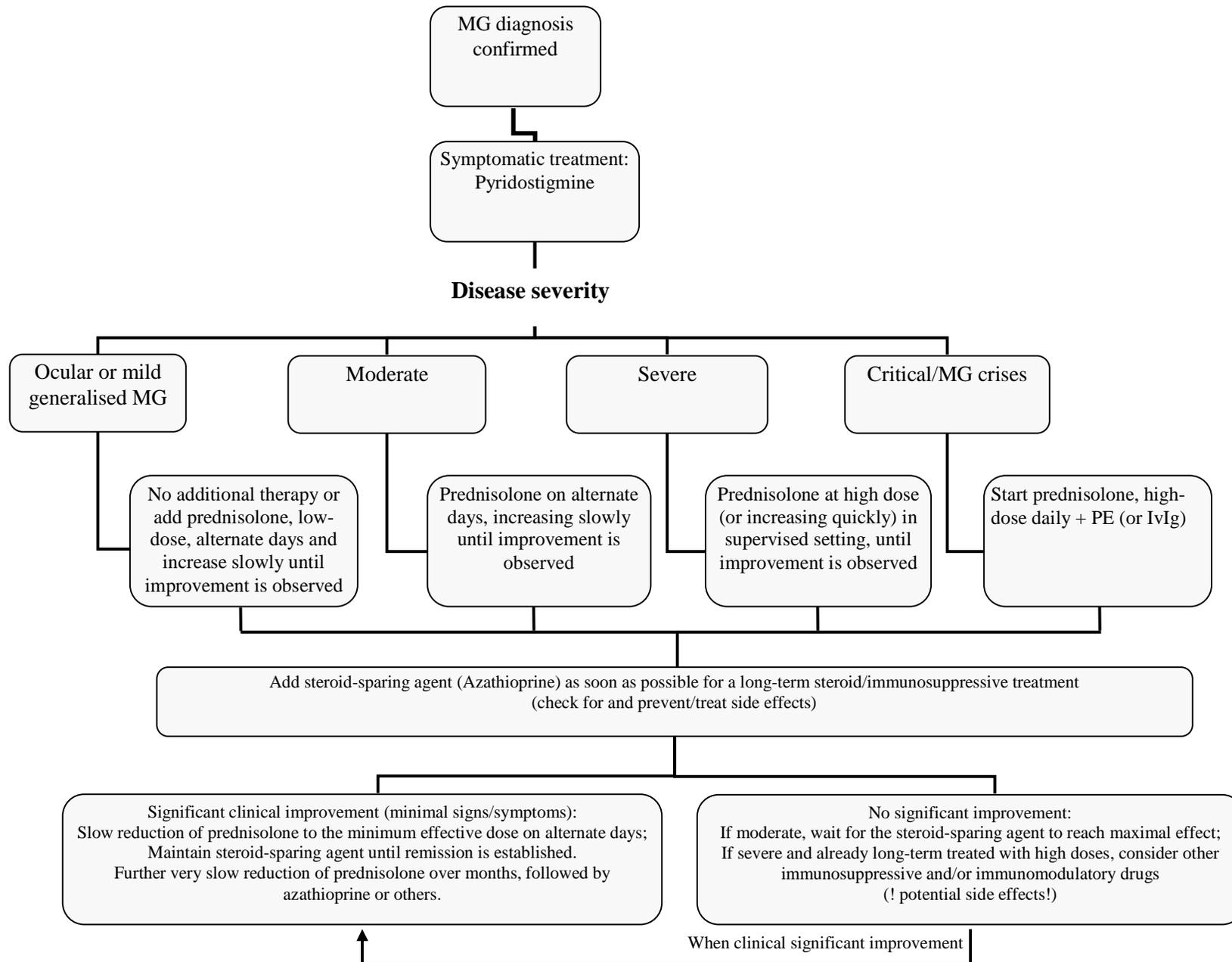
In all patients, it is vital to check MG symptoms, particularly those related to dysphagia and respiratory function, treatments followed and respective side effects (clinical and laboratory). The occurrence of other diseases (e.g. autoimmune and infections) and concomitant medications should also be monitored. It is also imperative to check for other conditions (e.g. surgical interventions, pregnancy and birth), which may interfere with MG or its treatment.

Patients who are more severely affected or vulnerable (e.g. the elderly), and those under particular circumstances (see above) who demonstrate a real or potential risk of MG crisis need even closer supervision and probably hospital admission for monitoring and treatment adjustments. Therefore, these patients should be referred early to an MG centre or neurologist or to the hospital,

It is also important to review closely patients recently diagnosed and starting their treatment (e.g. increasing dose of steroid), to check their improvement, to monitor early side effects of medications, and to help them cope with the difficulties related to a newly diagnosed chronic disease.

Less concerning, but also worthy of attention are patients with longstanding, mild, and stable MG, whose neurologist considers to start reducing their medication. Those patients also need regular visits or to communicate by phone with their GP, a nurse, or their neurologist to make sure that they do not relapse. If any sign of worsening happens without any other reason, their medication plan should be reviewed and possibly the doses increased.

2.3 Treatment flowchart for MG



2.4 Table: Summary of the most commonly used treatments in MG

	Indications	Advantages	Disadvantages/Side effects	Monitor	Usual adult doses
Pyridostigmine (Mestinon)	First-line treatment in most MG patients	Few serious side effects	Cholinergic symptoms (nicotinic and muscarinic) and crisis		Up to 60 mg five times a day
Prednisolone	Significant disability due to disease symptoms; Effective long-term immunosuppression; Relatively rapid effect desired	Short onset of action (1 to 3 months); Effective in most patients; Can be used in pregnancy	Transient <i>initial</i> severe exacerbation (1 to 3 weeks) <i>Main long-term side effects</i> Cushingoid features Weight gain Fluid retention Hypertension Diabetes Gastrointestinal haemorrhage and perforations Myopathy Avascular joint necrosis; Osteoporosis Acne; Striae Psychosis & Mood change Glaucoma, cataracts Increased susceptibility to infection	Weight, blood pressure, blood glucose and electrolytes, ocular exam, bones exam. Treat all patients with biophosphonate and antacids and additional medications according to occurring side effects	Moderate MG/outpatient: start with 10-15 mg on alternate days), increasing by 5 mg each 3-5 days until satisfactory clinical response achieved or maximum dose of 50-60 mg/day (or alternate days) reached. Slow taper should begin after 3-6 months of treatment and documented positive response. Severe MG/inpatient: start with (20-50 mg/day, increasing by 10 mg each 2-3 days to maximum 60-80 mg/day); may start with 60-100 mg/day. When improved and stable, slow taper to alternate days and then reduce dose to the lowest possible dose.
Azathioprine	Long-term immunosuppression Steroid sparing Minimize steroid side effects	Well known and relatively safe drug	Long onset of action (6 to 12 months) and of maximal benefit (up to 24 months) Possibly increased risk of malignancy§ Reduced RBC, WBC, platelets (dose related or idiosyncratic) Flu-like symptoms Gastrointestinal disturbances, pancreatitis Liver dysfunction	Hb, platelets; WBC, Liver function	Initial: 2.5 to 3 mg/kg once daily Maintenance: 1.5 to 2.5 mg/kg once daily
Mycophenolate mofetil	Long-term immunosuppression in patients intolerant or unresponsive to Azathioprine	?Shorter onset of action? (2 to 12 months) Few side effects: Low risk for late malignancies; No major organ toxicity	High Cost Limited experience of utilization in MG Infections Gastrointestinal problems Renal dysfunction	Blood counts, Renal function	Usual dose: 1 g twice daily

	Indications	Advantages	Disadvantages/Side effects	Monitor	Usual adult doses
Cyclosporine A	Long-term immunosuppression Especially/only when prednisone or azathioprine cannot be used or are ineffective When relatively rapid response (months) is desired	Short onset of action (1 to 3 months)	Serious side effects (most are dose related) Nephrotoxicity Hypertension ?Increased risk of malignancy Teratogenic Many drug interactions: especially avoid: NSAIDs; Amphotericin B and nephrotoxic drugs High cost Needs serum level monitoring	Renal function; Blood pressure Blood level: 12 hours after previous dose	Initial: 2.5 mg/kg, divided up into two doses daily Maintenance: lowest effective dose (may be effective below "therapeutic range" in serum)
Cyclophosphamide	Severe MG in patients intolerant or unresponsive to steroids and all the other immunosuppressive agents		Potentially serious, acute or long-term side effects Nausea, vomiting and diarrhea Mouth sores Bone marrow suppression Opportunistic infections Bladder toxicity Sterility Cardiotoxicity Neoplasms Interfere with other drugs	Complete blood count (CBC) Urine exam Kidneys and liver function	Variable dosages used. 1-2 mg/kg/d in one series 3-5 mg/kg/d in another. Some patients treated with 200-250 mg IV for 5 d
Plasma Exchange	Acutely ill MG patient Pre-thymectomy in patient with respiratory or bulbar involvement NOT for long-term treatment	Very short onset of action (3 to 10 days) Probably more effective in crisis than human immune globulin	Requires specialized equipment & personnel Complications more frequent in elderly More side effects than human immune globulin	Vital signs during PE; Check for fluid overload or hypovolemia	5 exchanges over 9 to 10 days.
Intravenous Immunoglobulin	Acutely ill MG patient ?Chronic use in severe disease unresponsive to other therapies	Easily administered: Widely available; Rare serious side effects	High cost Probably less effective in crisis than PE May increase serum viscosity and thromboembolic events Headaches and rare aseptic meningitis Cost is virtually the same as PE	Vital signs and allergy features during and after perfusion; Check for fluid overload	2 grams/kg (over 2 to 5 days); repeat every 4-6 weeks if in a long-term regime

§: Not demonstrated in MG patients except for basal cell and squamous cell skin cancers

Most of the recommendations in 1. and 2. have been classified as "good practice point" or "level A or B recommendations"

2.5 Drugs and toxins that adversely affect myasthenia gravis

Adrenocorticosteroids and ACTH; Thyroid preparations

Neuromuscular blocking agents (including Botulinum toxin), anesthetic agents; alcohol

Antiarrhythmics: quinidine, procainamide, phenytoin, gabapentin, verapamil, intravenous lidocaine or procaine

Antibiotics:

Telithromycin (Ketek®) (contra-indicated in MG)

Aminoglycosides: systemic gentamicin, tobramycin, neomycin, paromomycin, amikacin, kanamycin, streptomycin

Polypeptides: polymyxin B, colistin, colisthemethate Tetracyclines: chlortetracycline, oxytetracycline, tetracycline, demeclocycline, methacycline, doxycycline, minocycline

Miscellaneous: clindamycin, lincomycin, ciprofloxacin, high-dose ampicillin

Intravenous erythromycin D-Penicillamine, trimethadione, chloroquine, alpha-interferon, interleukin-2

Beta-blockers including timolol maleate eyedrops, trihexyphenidyl hydrochloride, hydroxymethylglutaryl-coenzyme A reductase inhibitors (“statins”)

Cimetidine, citrate, chloroquine, cocaine, diazepam, lithium carbonate, quinine,

Radiocontrast media (iothalamic acid, meglumide diatrizoate); Gemfibrozil (Lopid)

Wasp stings, coral snake bite

2-6 Recommended literature

Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology*. 2003 Dec 23;61(12):1652-61.

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