CNNS

CLINICAL NEUROPHYSIOLOGY NEUROMUSCULAR SECTION

MYASTHENIA GRAVIS (MG):

Malaysian Consensus Statement

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Authors' note

This consensus serves as a quick reference to provide an easy explanation regarding MG to doctors and medical practitioners. We hope the important and updated information that has been included in this consensus will be beneficial to everyone treating patients with MG.

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Abbreviations

ACh, acetylcholine

AChR, acetylcholine receptor

BD, twice daily

BP, blood pressure

CT, computed tomography

CI, confidence interval

DEXA, dual X-ray absorptiometry

DM, diabetes mellitus

ELISA, enzyme-linked immunosorbent assay

EOD, every other day

IgG, immunoglobulin G

IL, interleukin

IV, intravenous

IVIg, intravenous immunoglobulin

LRP4, lipoprotein-receptor-related protein 4

MG, myasthenia gravis

MOA, mechanism of action

MRI, magnetic resonance imaging

MuSK, muscle-specific kinase

NMJ, neuromuscular junction

NPRA, National Pharmaceutical Regulatory Agency

OD, once daily

PET, positron emission tomography

QMG, quantitative MG score

QOL , quality of life

RCT, randomized controlled trial

SC, subcutaneous

TDS, three times a day

TPMT, thiopurine methyltransferase

URTI, upper respiratory tract infection

UTI, urinary tract infection

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Introduction and epidemiology of MG

- MG is a rare autoimmune disorder affecting the NMJ.[1]
- The hallmark of the disease is fluctuating weakness and fatigability of ocular, bulbar and limb muscles.[2,3]

Epidemiology of MG:

- Overall prevalence of **150–200 cases per million persons**[1]
- Estimated annual incidence of **8–10 cases per million person-years**[1]
- Prevalence of **<13 per 100,000 people** were reported by studies from China and Korea[1]

Bimodal distribution in **women**, with peak of disease onset around the age of **30 and 50 years**[2]

Incidence in **men** increases with age, with the highest rate between **60 and 89** years old[2]

In Malaysia, most patients with MG are **Chinese (58%)**, followed by Malays (28%), Indians (13%) and others (1%)[4]

Classified into different subgroups based on age of onset and association with different autoantibodies (**Table 1**)[1]

Classification and clinical features of MG

Table 1. Classification of MG subgroups[1,5*]

Types	Autoantibody	Subgroups	Age of onset (years)	Estimated frequency	Predominant thymic pathology
Generalized	AChR+[1]	Juvenile[2]	<18[2]	10–50%[2]	Hyperplasia[1,3]
		Early-onset MG (EOMG)[1]	<50[1]	Up to 70%[8]	Hyperplasia[1]
		Late-onset MG (LOMG)[1]	≥50[1]	Up to 24%[7]	Atrophy[1]
		Very late-onset MG[7]	≥65[7]	Up to 45%[7]	Normal[7]
		Thymomatous MG[1**]	Any[1]	10–15%[9]	Type AB and B thymoma[1]
	AChR-[1]	Anti-MuSK+ (MuSK-MG)[1]	Any[1]	5–8%[10]	Normal[1]
		Seronegative MG[1]	Any[1]	1–2%[11]	Variable[1]
		LRP4 MG[1]	Any[1]	1–2%[11]	Normal[1]
Ocular[***]	AChR, MuSK, LRP4 or none[1]	-	Any[1]	15%[12]	Variable[1]

*All patients can belong to only one subgroup at any given time.[1] Another subgroup, which is atypical MG, includes predominant distal limb weakness involvement in 3–7% of MG patients (commonly <50 years of age and AChR+) and dysphagia involvement in 15% of MG patients (commonly elderly and AChR+).[5,6,8,9] **About 30% of patients with a thymoma develop MG.[2] ***Ocular MG includes patients who exhibit only ocular symptoms without clinical weakness in other muscles, except orbicularis oculi.[1]

Clinical features of MG

Cardinal symptoms

The cardinal feature of MG is fatigable muscle weakness (**Figure 1**), which worsens with exercise and improves with rest.[2]

Other presenting symptoms and signs include:

- presence of diurnal variation and exercise-induced weakness, which provides strong clues to the diagnosis of MG across all subtypes[3]
- ocular muscles involvement, such as diplopia (double vision) and ptosis[2]

Ocular MG

- Inferior oblique muscle is most commonly affected, followed by lateral rectus and superior rectus muscles while superior oblique muscle is the least commonly affected.[14]
- Medial rectus muscle is usually the first muscle involved in ocular MG.[14] Rarely, vertical diplopia may be caused by isolated inferior oblique muscle palsy.[14]

Generalized symptoms

23% of the local patient population progress from ocular MG to generalized MG[4]

- The bulbar, neck, limb and truncal muscles can be involved in generalized disease.[1,2]

Ocular MG

- Ocular MG represents 15% of all MG cases.[12]
- About 85% of patients with ocular MG present with ocular involvement that can mimic every pupil-sparing pattern of ocular misalignment.[14,15] Ocular MG has to be differentiated from other complex ocular movement abnormalities, such as ocular motor nerve palsy or gaze palsy due to internuclear ophthalmoplegia (INO), Lutz posterior INO (or reverse INO) and one-and-a half syndrome.[15]

Other/atypical presentations

Symptoms	Comments
Predominant distal muscles involvement[2]	Weakness in wrist and finger muscles and foot drop
Isolated cranio-bulbar involvement[3]	In patients with MuSK-associated MG, many of these patients do not present with ocular symptoms
Partial dysgeusia[16]	• About 2.5% of patients with MG – both AChR antibodies and thymoma were present (notably, dysgeusia developed as the AChR antibodies increased) • Preceded motor symptoms in about 1.4% of patients • Although mostly limited to sweet taste, disturbances of other tastes have also been reported

- About 25% of MG patients switch between asymptomatic and symptomatic stages (fluctuations).[17]
- Myasthenic symptoms can be precipitated by infections and certain medications.[18,19] Please see Appendix 1 for full list of medications that can trigger or worsen myasthenic symptoms.

Figure 1. Clinical presentation of MG[2,9]

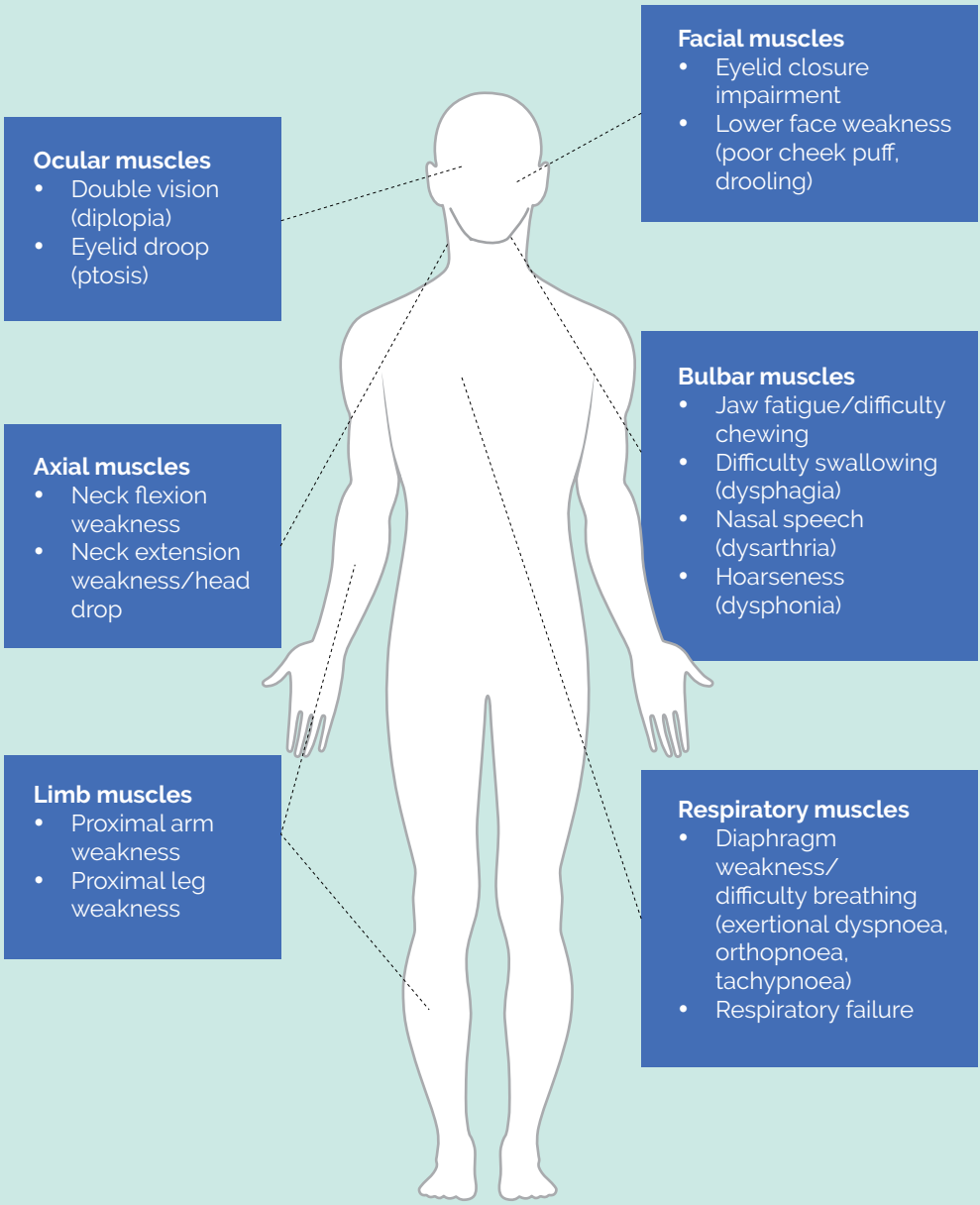
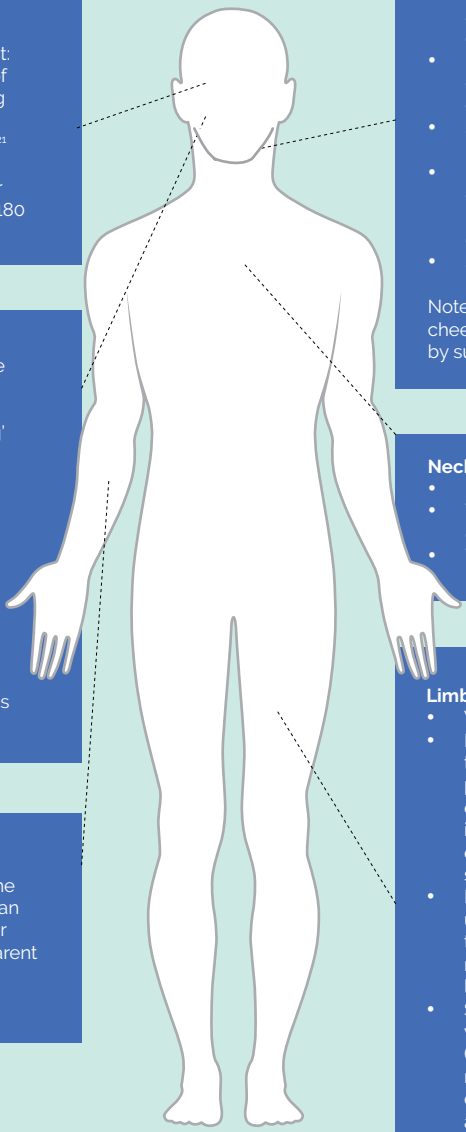


Figure 2. Clinical examinations and signs of MG[20–22]

Ocular findings
- Ptosis[20]
- Diplopia[20]
- Cogan's lid twitch test: Brief upward twitch of eyelid when returning to primary gaze from sustained downgaze[21]
- Positive 'fatigue' test: Increased ptosis after upward gaze for 60–180 secs[21]

Facial findings[20,21]
- Disappearance of the nasolabial fold and loss of expression producing a 'sagging' appearance
- Weakness in maintaining eyelid closure against the examiner's manual efforts to open them
- Horizontal smile or 'snarling' appearance when attempting to smile
- Difficult in puffing cheeks or pursing lips
- Bell's phenomenon

Limb findings*:
Arm (in sitting position)
Sustained abduction of the arms (120 secs); patient can no longer hold arms up or weakness becomes apparent with subsequent manual testing[21]



Bulbar findings
- Difficulty in chewing with pattern of weak jaw closure and relatively strong jaw opening[20,21]
- Difficult to swallow a glass of water without coughing or nasal regurgitation[20,21]
- Speech: Nasal, lingual, labial or hypophonic[20,21]
- Dysarthria may occur after counting 1–50. Note the number where dysarthria or nasality occurs[21]
- Single breath count test ≤25[21,22]

Note: Weakness of the neck or cheek muscles may be masked by supporting the jaw[21]

Neck and respiratory findings
- Drooping of the head[21]
- Weaker neck flexion than extension[20,21]
- Weak cough[20]

Limb findings*: Leg
- Weak hip flexion[20]
- Deep knee bends for 10–20 times with the patient's palm held in that of the examiner; an increase in pressure against the examiner's palm is an early sign of weakness[21]
- Rise from a chair without use of the hands for 10–20 times causing buttocks-first manoeuvre and body to lean forward[21]
- Sustained elevation of leg while lying supine (90 secs); patient can no longer hold leg up or weakness becomes apparent with subsequent manual testing[21]

*Not commonly done

Table 2. Clinical classification of MG according to the Myasthenia Gravis Foundation of America (MGFA)[23]

Class I	• Any ocular muscle weakness • May have weakness of eye closure • All other muscle strength 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 by 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)

Pathogenesis of MG

The most common underlying defect in MG is a decrease of available AChRs at the NMJs due to an antibody-mediated autoimmune attack.[24,25]

How does MG occur?

MG may occur either as a distinct primary immunological disease or as a paraneoplastic syndrome associated with thymic tumour.[24]

What role does the thymus play in the development of MG?

The thymus is **abnormal** in about **70–75%** of patients with MG

- In about 65%, the thymus is 'hyperplastic', with the presence of active germinal centres detected histologically, though the hyperplastic thymus is not necessarily enlarged[24,26]

About **10–15%** of patients have thymic **tumour** (thymoma)

- Muscle-like cells within the thymus (myoid cells), which bear AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland[24]

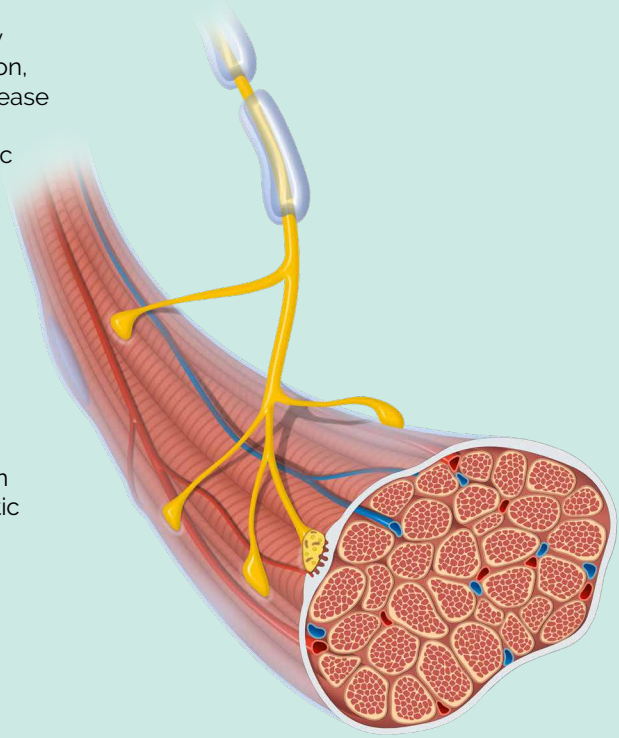
Impairment of central thymic and peripheral self-tolerance mechanisms is postulated to **mediate an autoimmune $CD4^+$ T cell-mediated B cell activation and synthesis of pathogenic high-affinity autoantibodies** of either IgG1 or IgG3 subclass that target components of the NMJ[24,25]

What are the key mechanisms underlying the muscle weakness and fatigue observed in MG?

1. The fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane[25]
2. Postsynaptic folds are flattened or simplified[27]

→ Reduced efficiency of neuromuscular transmission[27] → Small end-plate potentials that may fail to initiate muscle action potentials[27]

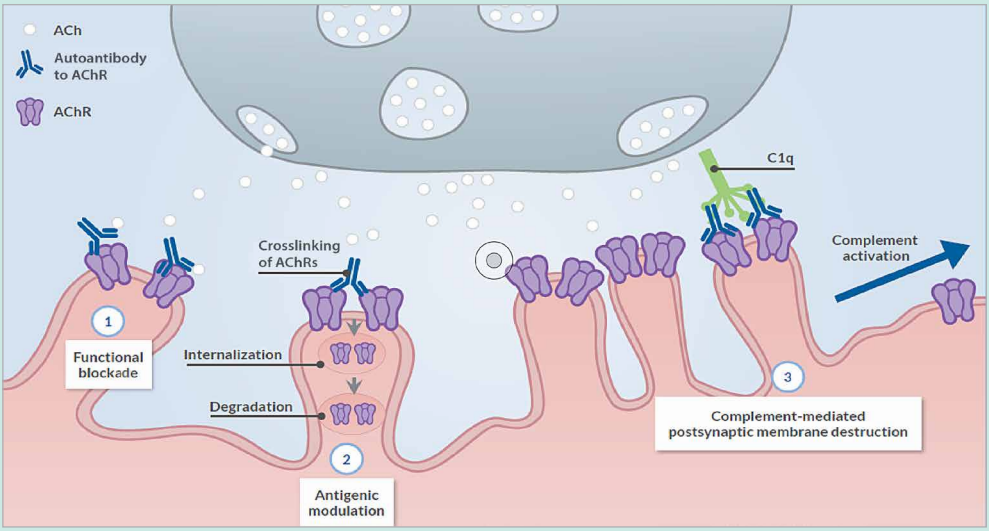
- In MG, the reduced efficiency of neuromuscular transmission, along with decline in ACh release per impulse during repeated activity (known as presynaptic rundown), leads to activation of fewer muscle fibres by successive nerve impulses.[27]
- This progressive decline contributes to increasing weakness and myasthenic fatigue observed in MG patients.[17] Additionally, this mechanism explains the decremental response seen in repetitive nerve stimulation (RNS) during electrodiagnostic testing.[27]



How do different subtypes of autoantibodies in MG affect neuromuscular transmission and what are their clinical implications?

- There are several subtypes of MG based on the specific antigens targeted by autoantibodies.[11,28,29] These antibodies bind to the nicotinic AChR, MuSK, LRP4 and agrin, which play roles in AChR clustering and neuromuscular synapse maintenance (**Table 3**).[11,28–31]
- AChR antibodies are typically IgG1 and IgG3 subclasses in humans, which can cause complement-mediated attack and dimeric binding to adjacent AChRs on the muscle surface, thus accelerating their internalization.[25] This process reduces available AChRs *via* three mechanisms (**Figure 3**)[25,27]:
    - blockade of active site of the AChR, ie, the site that normally binds ACh;
    - cross-linking of AChRs, leading to accelerated internalization, endocytosis and degradation of the AChR; and
    - activation of complement cascade, leading to formation of membrane attack complex (MAC) and destruction of postsynaptic membrane at the NMJ.
- A small fraction of patients does not have detectable circulating autoantibodies to known targets.[25] Accordingly, these patients are diagnosed as having seronegative MG.[25]
    - Around 15% are known to be double-seronegative, where they do not have antibodies against either AChR or MuSK – up to 27% of them have LRP4 antibodies detected.[3,7]
- Among the subtypes, late-onset MG is associated with the most favourable prognosis, followed by early-onset MG/MuSK MG and seronegative MG/thymoma-associated MG.[17]

Figure 3. Binding of autoantibodies to AChRs leads to functional AChR blockade, cross-linking AChRs and complement cascade activation[25,27]



Adapted from Gilhus NE, et al 2019.
ACh, acetylcholine; AChR, acetylcholine receptor; C1q, complement component 1q

Table 3. MG classification by autoantibodies and associated clinical features[2,7,11,17,28,29,32–35]

Autoantibody target	Antibody isotypes	Subtypes	Distinctive clinical features
AChR[11,28]	• IgG1[28] • IgG3[28] • HLA-B8-DR3[2]	Early-onset[11,28]	Female predominance; most likely to present with an initial generalized disease; favourable prognosis; more responsive to thymectomy than late-onset[2,17,28]
		Late-onset[11,28]	Slight male predominance; ocular onset is the most common, followed by bulbar onset; 15% with thyroid disease; may have severe course; less responsive to thymectomy but may be more responsive to medications than early-onset[2,28,32,33]
		Very late-onset[7]	Ocular onset is common (43%); 94% have positive antibody test; <6% associated with thymoma
		Thymomatous[28]	Other paraneoplastic disorders
		Ocular[28]	Anti-AChR antibodies present in ~50% of patients
Clustered[28]	IgG	Generalized	Clinical course similar to that of non-thymomatous MG with anti-AChR antibodies
		Ocular	Similar to AChR ocular subtype above
MuSK[11,28]	• IgG4[28] • HLA-DRB1*14[32] • HLA-DQB1*05[32]	-	Median age of onset is 52 years; bulbar involvement appears in the first stage, with presenting symptoms of ptosis and diplopia; associated with tongue atrophy; typical fluctuations of myasthenic symptoms may not be evident; may have severe course; response rate of 47% to corticosteroids; favourable response to rituximab (RTX) but poor response to cholinesterase inhibitors and IVIg; not indicated for thymectomy[11,28,32,34,35]
LRP4[11,28]	IgG1[28]	-	Similar to AChR-MG, with similar response to treatment; favourable prognosis; may be found in patients who are anti-AChR+ and anti-MuSK+[11,28]
Agrin[28]	Unknown	-	May be found in patients who are anti-AChR+
Cortactin[28]	Unknown	-	May be found in patients who are anti-AChR+
Triple negative for AChR, MuSK and LRP4[29]	None	-	Similar to AChR-MG

Diagnostic investigations of MG

Overview of diagnostic methods of generalized MG[36,37]

Antibody assays	Neurophysiological tests	Supportive clinical tests
• Anti-AChR • Anti-MuSK	• RNS • Single-fibre electromyography (SFEMG) – single-fibre electrode (SFE)/concentric needle electrode (CNE)	• Eye ice-pack test • Oral pyridostigmine

Bedside clinical signs of ocular MG[38–41]

- Simpson test[38,39,41]
- Ice pack test[38–41]
- Heat test[38]
- Rest test[38–40]
- Cogan lid twitch test[39–41]
- Bienfang or forced eyelid closure test (FECT) [39,41]
- Lid-hopping sign[40,41]
- Eyelid retraction sign[40]
- Curtain sign[40,41]
- Paradoxical reversal of ptosis[40]
- Peek sign[40,41]

- The diagnosis of MG requires a combination of clinical history, physical examination and confirmatory tests.[36,37]
- Once MG is suspected on clinical ground, clinicians can proceed with specific antibody assays and/or neurophysiological tests.[37] In practice, concurrent bedside and neurophysiological tests with antibody testing are common as the results of antibody testing are usually delayed and many patients may have rapid progression to severe weakness or crisis.[9,22]

1.0 Antibody assays

1.1 AChR antibody

- About 85% of generalized MG and 50% of ocular MG have pathologic antibody towards the postsynaptic AChR.[42]
- The preferred standard method of testing is binding AChR antibody to a highly selective AChR agonist (eg, bungarotoxin) using radioimmunoprecipitation assay (RIPA).[42] Using this method, the specificity is extremely high and false positive result is exceedingly rare (**Table 4**).[42,43]
- The more easily available assay is ELISA, but it has lower sensitivity and specificity than RIPA (**Table 4**).[31,37] In one study, only two-thirds of RIPA-positive assays are tested positive using ELISA method.[42]
- The antibody level correlates poorly with disease activity or severity.[44] Hence, the titre should not be used to guide treatment decision.[42]
- In a retrospective study that determined the positive predictive value (PPV) and risk of false AChR-IgG positivity with RIPA in a large cohort of patients with suspected MG, false AChR-IgG positivity may occur in clinical practice with RIPA (13.8%) and is associated with a low antibody titre.[45] The PPV and specificity were 86.2% (95% CI, 82.2–89.6) and 98.9 (95% CI, 98.5–99.2), respectively.[45]
- Caution is needed when titres between 0.5 and 0.9 nmol/L are detected in low-probability situations and were more likely to become seronegative on subsequent tests because failure to recognize false antibody positivity may lead to misdiagnosis and inappropriate treatments.[45]
- After stratification by titre ≥1 nmol/L, the PPV increased to 96.6% (95% CI, 94–98.3).[45] In the study, serum of 7 non-myasthenic patients was re-tested by cell-based assay (CBA), giving negative results (n=6) or selective positivity against the foetal AChR isoform (n=1).[45]

1.2 MuSK antibody

- In patients who are seronegative to AChR antibody, 40–70% of them have MuSK antibody.[46] It represents around 6–8% of all MG patients.[37]
- MuSK antibodies are of IgG4 isotype and hence, do not activate complements.[30] MuSK antibodies block MuSK signalling and LRP4 binding to MuSK.[30] As a result, AChR clustering is disturbed.[30] Besides its characteristic phenotype, thymic abnormalities are generally not observed in this group.[30]
- MuSK antibody level is routinely measured by the RIPA.[37] Low-affinity MuSK antibodies can now be detected using CBA (**Table 4**).[43,47] Interestingly, MuSK antibody level has been shown to correlate with disease severity, in contrast to AChR-MG.[47] However, routine follow-up with MuSK antibody level is not typically performed.[37]

1.3 Dual seronegative MG (dSNMG)

- By strict definition, patients with no detectable AChR and MuSK antibodies *via* the RIPA are considered dSNMG patients.[48,49] Patients with dSNMG represent a rather heterogenous group with no significant difference to the seropositive group.[49]
  - In one study, 16 out of 42 (38.1%) patients with RIPA-negative MG were positive for clustered AChR antibodies using CBA, with 100% specificity.[48] This group of patients had childhood-onset MG, milder-in-severity and predominantly ocular symptoms.[48] In another study, up to 66% of RIPA-negative MG patients harboured clustered AChR antibodies using CBA.[49]
  - MUSK antibody was detected in 8% of dSNMG patients using CBA.[50]
  - LRP4 antibody was detected in up to 19% (ranging from 7–33%) of patients with dSNMG and in about 27% of those with ocular phenotype.[51]
  - In cases with high clinical suspicion of MG but non-diagnostic investigations of dSNMG, consider testing the serum using CBA method.[47] (Currently only available in selected overseas laboratory centres)

Table 4. Antibody assays by sensitivity and specificity for MG diagnosis[43]

Antibody assays	Sensitivity (%)	Specificity (%)
AChR antibody		
• **RIPA**	64.1	97.8
• **ELISA**	62.7	94.8
• **CBA**	72.3	97.8
MuSK antibody		
• **RIPA**	2.4	100.0
• **ELISA**	2.6	99.1
• **CBA**	2.9	100.0

2.0 Neurophysiological tests

These are electrodiagnostic tests that comprise of specialized machines, electrodes and needles.[37] These are available in most centres with neurology service and should be done by trained personnel.[12,37] Patients should be assessed by the treating clinician prior to the tests to determine pre-test probability of having MG.[36] This is important as the following tests are aimed at weak muscles detected clinically.[37]

Many conditions may result in abnormal neurophysiological tests (**Table 5**).[37,52–55] However, neurophysiological tests play an important role in the diagnosis of MG especially in seronegative cases as the sensitivity of serology in detecting MG is not as high as its specificity.[37] In addition, these tests are useful to clinch the diagnosis early while waiting for the serology result.[9]

Table 5. Conditions that can cause abnormal neurophysiological tests (decremental response in RNS or abnormal jitter in SFEMG)[37,52–55]

- Congenital myasthenic syndrome[52]
- Myotonia spectrum disorders[53]
- Presynaptic neuromuscular junction diseases (NMJDs) (eg, Lambert-Eaton myasthenic syndrome, botulism, anti-GQ1b syndrome [Miller Fisher spectrum])[52,54]
- Active neurogenic denervation & reinnervation disorders (eg, amyotrophic lateral sclerosis, Kennedy's disease)[37,55]
- Others (eg. organophosphate poisoning)[52]

Note: Technical factors need to be excluded.

2.1 RNS

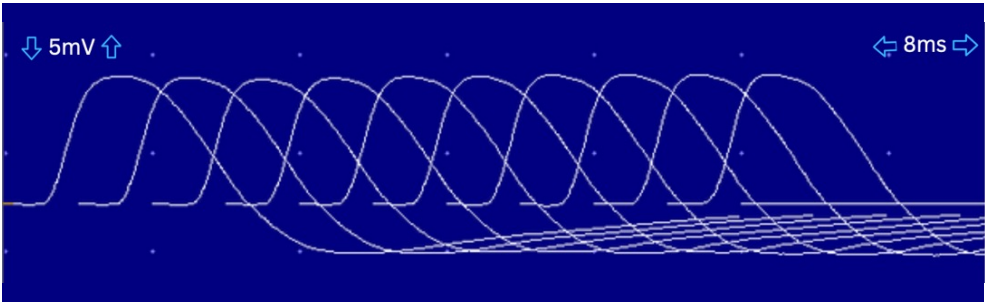
- In cases suspicious of MG, RNS at slow rate, ie, 2–3 Hz in short trains of 5–10 stimuli are often used in most centres.[56] In MG, some of the muscle fibre action potentials (MFAPs) fail to reach threshold with successive volleys of ACh molecules that are released at the terminal motor neuron.[37] This results in a characteristic decremental response in the compound motor action potential (CMAP) train of stimuli.[37]
- The result is considered abnormal if there is a reproducible CMAP decremental response of >10% comparing the 4th to the 1st supramaximal responses (**Figure 4**).[52] Due to mobilization of secondary stores, there is a mild increment in CMAP amplitudes in the subsequent stimuli seen after the 5th response, producing a 'U' or saddle shape pattern which is characteristic of MG.[37,52]
    - Normal muscle function is not affected due to the neuromuscular system's high safety margin.[37] However, a technical artefact can cause up to a 10% decrement in signal, which many laboratories still consider normal.[37] However, some may view a decrement >7% or even 5% as abnormal if artefacts are ruled out.[37] Abnormal reference values for RNS of facial and proximal muscles are summarized in **Table 6**.[57]

Table 6. Abnormal decremental values for RNS testing of uncommon muscles involved in MG[57]

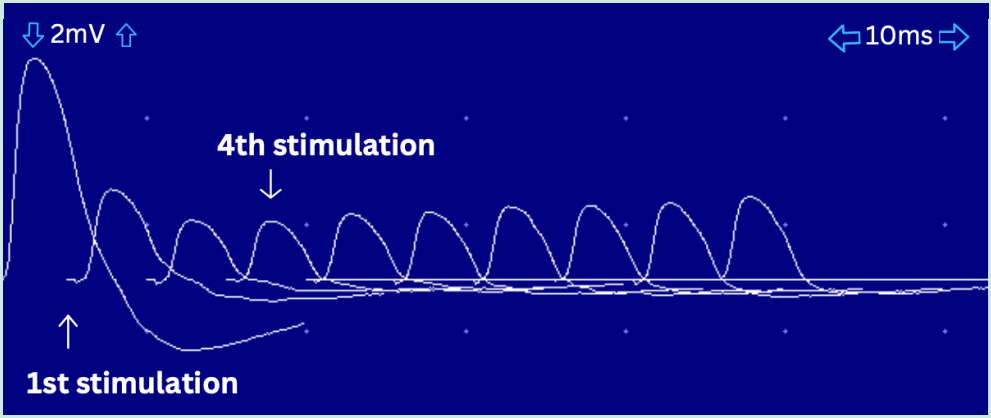
Muscles	Methods	Abnormal % decrement (amplitude)
Diaphragm	• Pre- and post-maximum voluntary contraction (MVC) • Held breath	• >11% • >15%
Masseter	Rest and post-MVC	>8%
Tongue	Rest and post-MVC	>11%
Serratus anterior	Rest and post-MVC	>9.4%

- RNS has been consistently shown to have high specificity in both ocular and generalized MG.[37] In generalized MG, the RNS has sensitivity of up to 80%.[38,58] However, the sensitivity of RNS in ocular MG is low (up to 30%) (**Table 7**).[58] Hence, a normal RNS cannot exclude MG, particularly ocular MG, in which case, jitter analysis is recommended instead.[59]
- The diagnosis yield is highest by recording from the clinically affected muscles.[37] In addition, it has been shown that there is a 5–7% further increase in sensitivity by repeating the test post-exercise to demonstrate the post-exercise exhaustion phenomenon.[60]
- Of note, pyridostigmine is generally stopped 24 hours prior to the test as it can mask the NMJ defect.[52]

Figure 4. Normal RNS of the left nasalis at the rate of 3 Hz



Abnormal RNS of the left trapezius muscle at the rate of 2 Hz demonstrating significant CMAP decrement of 73% between the first and fourth potentials



2.2 SFEMG – SFE/CNE

- SFEMG is the most sensitive test to demonstrate disturbed neuromuscular transmission in adults.[60] It is abnormal in 95–100% of patients with generalized MG and 88% of patients with ocular MG (**Table 7**).[61]

SFEMG is non-specific because it can be abnormal in other neurogenic conditions, such as radiculopathy and motor neuron disease, myogenic condition and recent botulinum toxin use.[37,62]

- SFEMG is a valuable test especially in the setting of mild or ocular MG where antibody assay and RNS test are often normal.[37] Also, a normal SFEMG in a weak muscle can essentially exclude MG as the underlying aetiology.[37]
- However, due to cost and hygiene purposes, SFE is not available in many countries and hence, CNE is widely used instead.[63]
- As CNE recording pick-up area is much larger, the recorded spike is produced by more than one muscle fibre.[63] Hence, by strict definition, this is not single-fibre recording but rather it is referred to as 'apparent single-fibre action potentials (ASFAPs)'.[63]

- There are two techniques – volitional (voluntary activation) jitter analysis and stimulated (electrical stimulation) jitter analysis.[37] Jitter represents the variation in the time interval or latency between two ASFAPs (voluntary technique) or between the stimulus and the response (stimulated technique).[61,62] The time interval or latency represents the time for the end-plate potentials (EPPs) to reach the firing threshold (**Figure 5**).[64] In MG, the latency is prolonged and if the EPPs do not reach the threshold, blocking phenomenon occurs (**Figure 6**).[64]
- However, jitter analysis has several disadvantages – the test is time-consuming, prone for technical issues and not readily available in all hospitals.[62] Sensitivities of different electrodes with different techniques, however, are not significantly dissimilar (**Table 7**).[61,62] Reference jitter values for CNE and SFE are shown in **Table 8**.[65]

Figure 5. Stimulated jitter analysis of the left orbicularis oculi demonstrating normal muscle fibre potential with jitter of 10 µs

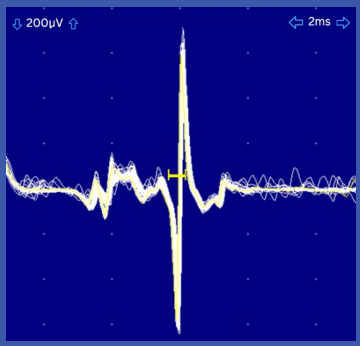


Figure 6. Stimulated jitter analysis of the left orbicularis oculi demonstrating abnormal muscle fibre potential with increased jitter value of 72 µs and concomitant blockings

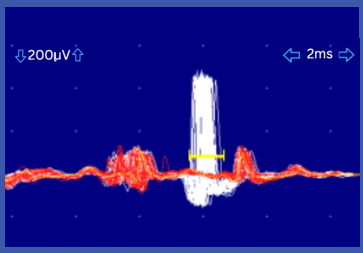


Table 7. Neurophysiological tests by sensitivity and specificity for MG diagnosis[37,58,61,62]

Neurophysiological tests	Sensitivity (%)	Specificity (%)
RNS[37,58] • **Generalized MG** • **Ocular MG**	 80 30	 94–97 94–97
SFEMG (SFE)[61,62] • **Generalized MG** • **Ocular MG**	 95–100 88	 70–97 (generalized or ocular)
SFEMG (CNE)[62] • **Generalized MG** • **Ocular MG**	 75–100 62–93	 96–100 (generalized or ocular)

Table 8. Reference jitter values (µs) for CNE and SFE[65]

Electrode	Orbicularis oculi		Frontalis		Extensor digitorum	
	CNE	SFE	CNE	SFE	CNE	SFE
Voluntary activation						
Mean jitter	31	40	28	34	30	35
Individual jitter	45	55	38	51	43	50
Stimulation activation						
Mean jitter	27	20	21	23	24	25
Individual jitter	36	30	28	35	35	40

Table 9. American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Guidelines and European Standardized Telematic tool to Evaluate Electrodiagnostic Methods (ESTEEM) group recommendations for electrodiagnostic examination of neuromuscular transmission disorders[66]

	AANEM Guidelines	ESTEEM recommendations
Combining RNS and SFEMG	No	Yes
Criteria for abnormal neuromuscular transmission failure	≥1 abnormal RNS or ≥1 abnormal SFEMG	≥2 abnormal RNS if no abnormal SFEMG or ≥1 abnormal RNS if ≥1 abnormal SFEMG or ≥2 abnormal SFEMG
Criteria for the definition of decrement	≥10% decrement	Abnormal decrement according to the laboratory's local reference value

Optional AANEM SFEMG criteria: 1) For patients with mild or solely ocular symptoms and RNS believed to be normal, or if discomfort prevents completion of RNS, SFEMG may be performed as the initial test; 2) In laboratories with SFEMG capability, SFEMG may be performed as the initial test for disorders of neuromuscular transmission

3.0 Supportive clinical tests

The ice pack test and assessment of clinical response to cholinesterase inhibitors may support clinical suspicion of MG.[37] These are at best supportive findings rather than confirmatory of MG.[37]

3.1 Ice pack test

- Patients with MG experienced worsening fatigue and weakness in response to heat, whereas cold had the opposite effect of improving these symptoms.[37]
- The ice pack test is a non-invasive, inexpensive and rather quick test to perform in the clinic.[67,68] It is most useful in differentiating partial ptosis due to MG from other mimics.[67]
- Despite being a simple test, the following steps are to be observed accordingly[69,70]:

1. With patient seated and relaxed and **eyes in primary gaze**, apply digital pressure to the frontalis muscle
2. **Measure the margin reflex distance** in the centre of the pupils using a millimetre ruler with eyes in primary gaze fixated at a point on the wall
3. **Apply ice pack** or ice-filled surgical glove to the most affected eyelid for 2 minutes (instruct the patient to gently close the eyelid and avoid excessive pressure)
4. **Measure the margin reflex distance within 10 seconds** after removal of ice pack

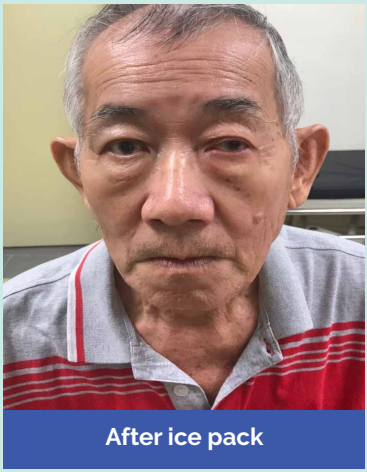
- An ice pack test that is considered positive is an improvement of >2 mm in margin reflex distance (**Figure 7**).[67,69] Ice pack test gives a sensitivity of 86% and specificity of up to 79%.[67] Evidence has shown that by repeating the ice pack test at a different day, it increases the sensitivity further.[70]
  - In addition, a study involving a large Asian cohort showed that combining a positive ice pack test with an abnormal SFEMG further improves the specificity of MG diagnosis.[71]
- However, caution needs to be taken in applying the test in patients with complete ptosis and isolated diplopia.[68,70] Prolonged ice pack application can cause a false negative result as it leads to undesirable lower temperature that affects the contractile force of the muscle.[69]
- The median improvement of ptosis with rest test and ice pack test is about 2 mm and 4.5 mm, respectively.[38]
  - Compared with single ice pack test, repeating ice pack test further increases its sensitivity by 35%.[38]
  - Combining ice pack test with Simpson test for 2 minutes is more sensitive than ice pack test alone (**Table 10**).[38]

Table 10. Bedside screening tests by sensitivity and specificity for MG[38,41]

Tests	Sensitivity (%)	Specificity (%)
Ice pack[41]	20–90	30–100
Ice pack + Simpson test[38]	73	97
Cogan lid twitch test[41]	50–99	75–99
FECT[41]	94	91

Figure 7. A patient before and after ice pack test showing a positive test with an improvement of >2mm in margin reflex distance compared to the level of ptosis before the ice pack was applied[67,69]

Before ice pack

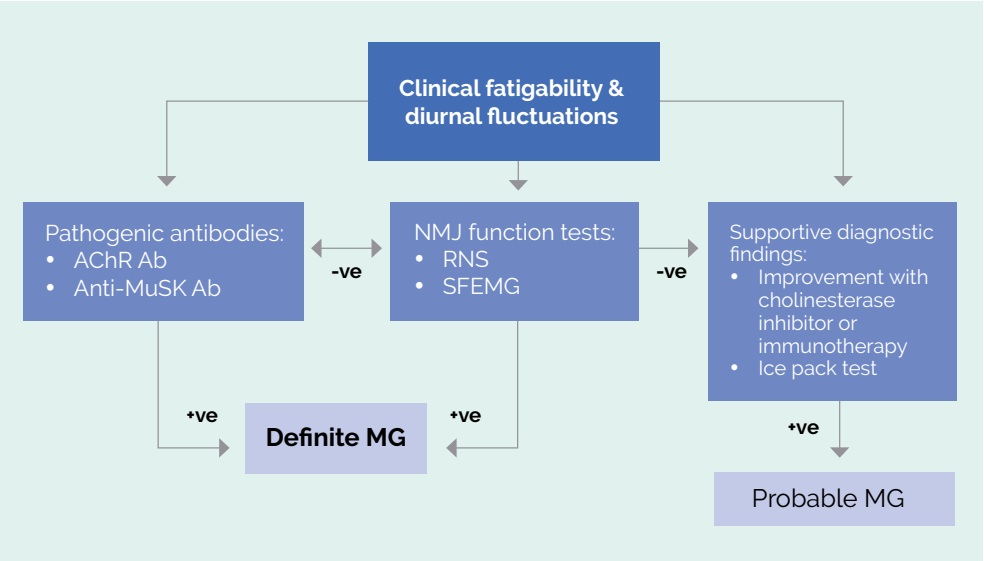


After ice pack

3.2 Response to cholinesterase inhibitors

- In the past, edrophonium bromide (Tensilon®) has been used as a diagnostic test in the clinic in some countries.[37] Tensilon® is administered intravenously and rapid symptom improvement can be seen within minutes.[37,72] However, this test has fallen out of favour in many countries due to safety concern and low availability of the drug. It also lacks of evidence of its diagnostic accuracy.[37,72]
- Clinicians can use oral pyridostigmine as an alternative to assess response.[72] In view of its longer half-life, clinicians can assess response to pyridostigmine 60 mg after 30–60 minutes.[73] Response to pyridostigmine can, at best, add diagnostic information but it is not confirmatory.[72]

Suggested algorithm for MG diagnosis[74]



4.0 Imaging

4.1 Thymus imaging

All patients with confirmed or probable MG should be screened for thymus abnormalities.[1] Pathologic thymic changes can be seen in >80% of generalized MG patients positive for AChR antibody.[75] About 50–60% of these patients have histological findings of follicular hyperplasia.[75] Up to 30% of patients with MG had thymoma.[75] Chest CT scan is the preferred modality in detecting thymoma.[76] Nevertheless, it has low sensitivity in detecting thymic hyperplasia.[1] Thymic abnormalities are extremely rare in MuSK-MG.[1]

Iodinated contrast agents can occasionally aggravate myasthenic weakness.[10] A study has shown that CT without contrast is not less sensitive than CT with contrast.[77] MRI chest is an alternative and it has been shown that MRI is better in delineating the location and invasiveness of the thymoma.[77]

4.2 Additional relevant investigations

Imaging of the brain and orbit

Not all ptosis and/or diplopia is due to MG.[78] In the setting of negative serology and normal neurophysiological findings, clinicians need to be aware of mimics such as inflammatory diseases, stroke and structural lesions.[78,79]

CT and MRI of the brain and orbit should be considered if confirmatory tests are normal.[78,80] PET may differentiate thymoma from thymic carcinoma.[81]

5.0 Thyroid function test

Thyroid function test should be done in all patients with MG.[37,82] A recent systematic review and meta-analysis showed that the pooled prevalence associated with thyroid function abnormalities in MG is about 6.8%.[82] Thyroid abnormalities can affect treatment efficacy as they mimic neuromuscular weakness.[83] Correction of thyroid disorders may improve some of the symptoms.[83] Caution should be taken for hyperthyroidism treatment, such as β-blockers, which can worsen myasthenic weakness.[83]

Treatment and management of MG

Overview of treatment modalities in the management of MG[1]

Symptomatic treatment	Oral immunosuppressants	Immunotherapy	Surgery	Other therapeutic classes
Cholinesterase inhibitors (eg, pyridostigmine bromide)	• Corticosteroids • Azathioprine • Mycophenolate mofetil • Calcineurin inhibitors (eg, ciclosporin and tacrolimus) • Methotrexate	• Plasmapheresis • IVIg	Thymectomy	• Cyclophosphamide • B cell-targeting therapies (eg, RTX) • Terminal complement activation inhibitors (eg, eculizumab and ravulizumab) • Neonatal Fc-receptor (FcRn) antagonists (eg, efgartigimod and rozanolixizumab)

1.0 Symptomatic therapy

1.1 Cholinesterase inhibitors

- Cholinesterase inhibitors (eg, pyridostigmine bromide) remain the first-line treatment in patients with MG.[9]
- Oral cholinesterase inhibitors prevent the enzyme acetylcholinesterase from breaking down the neurotransmitter ACh into choline and acetate, increasing the amount of ACh available for binding in the NMJ.[9,84]
- Patients with solely ocular symptoms or non-progressive mild disease may only need cholinesterase inhibitors for symptoms control.[9]
- Cholinesterase inhibitors do not affect disease progression.[9]
- At a very high dose (>450 mg daily), pyridostigmine bromide can precipitate paradoxical increase in weakness due to depolarization block of NMJ.[9]
- In terms of disease type, patients with MuSK-MG demonstrate poor response to pyridostigmine bromide while juvenile patients with MG may have a robust cholinesterase-inhibiting response.[85–87] In terms of disease presentation, patients with limb and bulbar symptoms respond better to cholinesterase inhibitors than those with ocular manifestations; patients who have trouble chewing or mild dysphagia are advised to take pyridostigmine 30 mins before a meal.[88]
- Side effect management includes[88]:
  - Titrate up slowly every 2 to 3 days from common starting dosage of pyridostigmine 30 mg TDS
  - Take pyridostigmine with food
  - Use of oral anticholinergic drugs that have little to no effect on nicotinic receptors (eg, glycopyrrolate 1 mg, propantheline 15 mg and hyoscyamine sulfate 0.125 mg) either prophylactically or with each pyridostigmine dose

2.0 Oral immunosuppressants

2.1 Corticosteroids

- The exact MOA of corticosteroids in MG remains unknown, but it was postulated that corticosteroids have a broad inhibitor effect on immune system *via* the reductions of endothelial adhesion of leukocytes and production of inflammatory cytokines.[84]
- Prednisolone is usually initiated when the symptoms of generalized or ocular MG are not sufficiently controlled by cholinesterase inhibitors alone.[77]
- Common obstacles of corticosteroid therapy are frequent MG relapses following tapering of treatment and risk of side effects, especially given as prolonged treatment.[89]
- There are two common clinical approaches to oral prednisolone administration, namely high-dose, rapid treatment induction regimen and low-dose, slow titration regimen (**Table 11**).[84]
    - Nearly one-third of patients may develop temporary exacerbation of symptoms within 7–10 days of starting high-dose corticosteroids.[1] Patient subset with severe MG or marked bulbar involvement is at highest risk.[84] For patients with oropharyngeal or respiratory involvement, rapid modulating therapies, such as plasma exchange or IVIg, can be administered before the initiation of prednisolone to induce a rapid response as well as to prevent or reduce the severity of corticosteroid-induced exacerbations.[9]
    - High-dose corticosteroids should be used with caution during myasthenic crisis when the patient is on concomitant IVIg.[90]
    - Low-dose corticosteroids are used in the outpatient setting.[76]
- Clinical remission of MG on corticosteroid treatment is defined as the absence of signs and symptoms after pyridostigmine is withdrawn.[76] Patients should only be considered for tapering down of steroid dose when they have achieved clinical remission for at least 2–3 months.[76]

Table 11. Comparisons of different corticosteroid regimens[9,84]

	High dose	Low dose
Dose initiation[84]	1.0–1.5 mg/kg/day over 2–4 weeks, followed by high daily or EOD dose for another 4–8 weeks	10 mg/day, increase by 10 mg every 5–7 days to peak dose of 1.0–1.5 mg/kg/day
Indications[84]	Severe MG subset or marked bulbar involvement	Mild-to-moderate MG or MG with milder disability (eg, ocular MG)
Advantages	Rapid induction to achieve remission[84]	Lower risk of transient weakness during treatment inititation[9]
Disadvantages	Transient risk of symptoms exacerbation during treatment initiation[9]	Longer duration to achieve treatment response[84]

2.2 Azathioprine

- Azathioprine inhibits purine synthesis that interferes with T and B cell proliferation.[9]
- Azathioprine should be considered in patients with generalized or ocular MG who are steroid-dependent for symptoms control or patients who are relatively contraindicated for or experience severe side effects of corticosteroids (**Table 12**).[84]
- There is a postulation that long-term azathioprine use may increase the risk of certain malignancies and this is probably dose- and duration-dependent, hence a minimum effective maintenance dose is advised.[9]

2.3 Mycophenolate mofetil

- Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA) that depletes guanosine nucleotides preferentially in T and B cells, which inhibits their proliferation, leading to suppression of cell-mediated immune responses and antibody formation.[9,84,91]

- Mycophenolate mofetil acts as a steroid-sparing agent (**Table 12**).[84] Several retrospective studies have suggested its robust response of disease control of around 70% in MG patients, with a favourable tolerability profile.[91,92]
- Mycophenolate mofetil is contraindicated during pregnancy owing to the risk of teratogenicity and high risk of miscarriage in the first trimester (**Table 12**).[84] Patients should use contraception during its use and for at least 6 weeks after cessation of the drug.[76]

2.4 Calcineurin inhibitors

- Ciclosporin is a calcineurin inhibitor that suppresses cytokine secretion and interferes with T cell proliferation.[9,84] It is used mainly as a steroid-sparing agent in MG patients in whom azathioprine is either ineffective or poorly tolerated (**Table 12**).[9] The efficacy of ciclosporin in MG was supported by two small double-blind, RCTs.[93,94]
- Tacrolimus (FK506), with a similar MOA as ciclosporin, also has beneficial effects in MG patients (**Table 12**).[17,95,96]

2.5 Methotrexate

- Methotrexate is a type of folate antimetabolite.[84] It is indicated as part of chemotherapy regimen at high doses with its cytotoxic effect; at lower doses, it demonstrates immunomodulatory effect.[84] However, the use of methotrexate for MG is limited owing to the lack of convincing data of efficacy.[19] It was recommended that oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who are unable to tolerate or respond poorly to other steroid-sparing agents (**Table 12**).[19]
- Methotrexate is associated with a high risk of teratogenicity, hence it is strictly contraindicated in female patients planning for pregnancy (**Table 12**).[76,84] If the use of methotrexate is inevitable, patients should use contraception during the treatment course and for at least 3 months after stopping the drug.[76]

Table 12. Choices of oral therapies and their potential adverse effects in MG patients[4,9,19,28,76,84,89,93,97,98]

	Dosing initiation and frequency	Onset of action	Use in MG	Disease monitoring	Potential adverse effects
Pyridostigmine	15–30 mg every 4–6 hours[9]	15–30 mins[84]	First-line symptomatic relief[9]	Nil[84]	Abdominal cramps, diarrhoea and flatulence; if overdose, cholinergic crisis may occur (presents with hypersalivation, bradycardia, hyperhidrosis, lacrimation and miosis)[9,84]
Prednisolone	High-dose, rapid induction vs. low-dose, slow titration (refer to Table 11)[84]	3–6 weeks[28]	First-line immune therapy[28]	Regular BP monitoring, glucose screening, weight management, annual eye assessment and DEXA scan[9,84]	Hypertension, impaired glucose tolerance, abnormal lipid profile, weight gain, peptic ulcer disease, steroid-induced myopathy, tremor, cataract, glaucoma and osteoporosis[9,84,89]
Azathioprine	50 mg/day, titrate upward 50 mg every 2–4 weeks to achieve peak dose of 2–3 mg/kg/day[84]	6–12 months[28]	First-line steroid-sparing agent[28,84]	• Baseline and monthly full blood count and liver enzymes[84] • Baseline measurement of TPMT – dose reduction may be necessary in case of TPMT deficiency[76]	~32% (mainly bone marrow suppression, followed by liver dysfunction and opportunistic infections), others are influenza-like symptoms and malignancy (long-term use)[4,9,84]
Mycophenolate mofetil	500 mg BD, titrate until maximum dose of 3,000 mg daily[9,84]	4–12 months[28]	First-line steroid-sparing agent; widely used in the United States[28,76]	Baseline full blood count; monitor monthly during dose titration[9,84]	Bone marrow suppression and teratogenicity[9,84]

	Dosing initiation and frequency	Onset of action	Use in MG	Disease monitoring	Potential adverse effects
Ciclosporin	4–6 mg/kg in two divided doses[9]	2–3 months[28]	Steroid-sparing in patients intolerant or unresponsive to azathioprine or mycophenolate mofetil[9,28]	Trough levels (keep at <300 ng/mL), renal and liver function tests[84]	Hirsutism, tremor, gum hyperplasia, anaemia, hypertension and nephrotoxicity.[9,84,93] Dose adjustment is advised for patients with renal insufficiency[93]
Tacrolimus (FK506)	3–5 mg daily[9]	4–8 weeks[28]	Steroid-sparing in patients intolerant or unresponsive to azathioprine, mycophenolate mofetil or ciclosporin[28]	Same as ciclosporin[84]	Same as ciclosporin but with less nephrotoxicity[9]
Methotrexate	10 mg/week, titrate up 2.5 mg every 2 weeks up to maximum dose of 20 mg/week[84]	1–3 months[28]	When all other oral treatments have failed[19]	Full blood count and liver enzymes at least monthly[84]	Nausea, vomiting, stomatitis, alopecia, myelosuppression, hepatotoxicity, teratogenicity and pulmonary fibrosis.[76,84,97] Dose adjustment may be necessary in patients with renal impairment[98]

3.0 Thymectomy

- Thymectomy plays a central role in MG management based on the initial empirical observations that symptoms of MG patients improved after the procedure, which was confirmed with evidence from a recent landmark international RCT.[9,84,99]
- In patients with thymoma, thymectomy should be performed regardless of disease type and antibody status; tumour grade and staging will determine the need for further chemoradiation.[9,84] Myasthenic symptoms may or may not improve post-surgery.[84]
- In non-thymomatous patients, thymectomy should be considered early for patients with generalized MG or generalized AChR-MG if they are below the age of 50 years (especially if the latter group fails to respond to or cannot tolerate immunotherapy).[9,19,76,84]
- However, thymectomy in patients with positive MuSK, LRP4 or agrin antibodies is not recommended.[19,84,100]
- Thymectomy should be an elective procedure which is scheduled when the patient is neurologically stable owing to the peri-operative risk that may exacerbate myasthenic weakness.[84]

Pre-operative preparation	Operative methods	Postoperative assessment/ management
Immunosuppression • Plasma exchange or IVIg with or without steroids might be necessary in patients with oropharyngeal or respiratory weakness[9] • Maintain pre-operative anticholinesterase therapy regimen until the day of operation[101] **Lung function** Patients with pre-operative forced vital capacity (FVC) >2L or ≥65% mean FVC/peak FVC were shown to be less likely to experience postoperative myasthenic crisis[102]	Extended and partial, with either open, video-assisted or robot-assisted approach[103] • With comparable results, video-assisted and robotic thymectomy approaches have emerged as alternatives to conventional open approach due to shorter hospitalizations and limited morbidity[84]	**Immediate postoperative phase** • Cessation of anticholinesterase agents for 48 hours helps to reduce the occurrence of cholinergic crisis[101] • Predictor factors of myasthenic crisis include pre-operative factors of vital capacity (VC) of <2 L, bulbar symptoms, AChR antibody level of >100 nmol/L and history of pre-operative myasthenic crisis and intra-operative factor of blood loss of >1 L[101] • In case of myasthenic crisis, plasmapheresis[101] or IVIg is considered* **Remission** • 60% complete stable remission (CSR) in patients with thymus hyperplasia[104] • Thymomatous patients are associated with lower CSR, pharmacological remission and minimal manifestations, compared with non-thymomatous patients[105] • Patients with early-onset non-thymomatous MG are about twice more likely than their late-onset counterparts to achieve clinical remission[106]
		Follow-up PET is useful in excluding recurrence or metastasis in patients who underwent thymoma excision[81]
		Complications Thymectomy increased the rate of any type of autoimmune diseases by 2.7 times than non-thymectomy, in addition to the risk of cancer and all-cause mortality[107,108]
		Recurrence • Prevalence: About 18%[109] • Risk factors include older age, male gender, more severe disease, thymomatous MG, longer duration of MG before surgery and having an ectopic thymic tissue[109] • Significantly higher in thymomatous (33.3%) than non-thymomatous (20.8%) patients[109]

*Authors' own view

4.0 Myasthenic crisis

- Myasthenic crisis or impending crisis is defined as severe weakness from MG affecting bulbar and respiratory functions that necessitates mechanical ventilatory support.[2,9]
- Impending crisis is treated similarly as myasthenic crisis, with IVIg or plasma exchange as the mainstay treatment.[84]
- Very high doses of cholinesterase inhibitors can precipitate cholinergic crisis, causing a paradoxical increase in weakness with respiratory insufficiency.[84]

Clinical features of myasthenic crisis[18,84]

- Paradoxical breathing pattern, with shallow chest expansion – most reliable sign[18,84]
- Use of accessory muscles (sternocleidomastoid, scalene, intercostal and abdominal muscles)[18]
- Orthopnoea[84]
- Ophthalmoparesis and ptosis[18]
- Difficulty holding air within cheeks along with a 'myasthenic snarl' upon smiling[18]
- Incomplete jaw closure after chewing[18]
- Dysarthria, hoarse speech or dysphagia with nasal regurgitation[18]
- Weak cough[18]
- Weak neck flexion[18]
- Diaphoresis[84]

Predictors of progression to mechanical ventilation[110]

- Bulbar dysfunction
- Bilateral facial weakness
- VC <20 mL/kg
- Maximal inspiratory pressure (MIP) >-30 cm H_2O
- Maximal expiratory pressure (MEP) <40 cm H_2O
- Reduction by 30% in the absolute values of VC, MIP or MEP

Management of myasthenic crisis

- Withhold the use of cholinesterase inhibitors to avoid excessive secretions post-intubation that might complicate airway management and are not necessary to support vital functions.[9,76,84]
- Myasthenic crisis management requires rapid immunotherapy with either plasmapheresis or IVIg (**Table 13**).[84]
  - As the effects of IVIg or plasma exchange last only for several weeks, long-term immunosuppression should be intensified concurrently, most frequently with corticosteroid.[84]

Table 13. Choices of rapid immunotherapy in the treatment of myasthenic crisis[9,28,76,84,111,112]

	Plasmapheresis	IVIg
Types[111]	• Plasma exchange • Double filtration plasmapheresis • Immunoadsorption plasmapheresis	-
Uses	• Myasthenic crisis[111] • Maintenance therapy for refractory MG[111]	• Myasthenic crisis[76,84] • Patients with severe bulbar and respiratory symptoms[76,84]
Common dosing schedule	5 sessions on alternate days[111] • 5 sessions (daily or alternate-daily) may reduce circulating IgG and AChR antibodies up to 69% and 47%, respectively[112]	1–2 g/kg over 2–5 days (may be given as 0.5 g/kg for 2 days or 0.4 g/kg for 5 days)[9,76] • No evidence has demonstrated superiority of 1 g/kg vs. 2 g/kg for acute MG exacerbation[9,84]
Advantages	• Rapid onset of action (1–5 days)[9,28,84] • May benefit patients with risk factors for IVIg[76]	Improvement lasts for 4–8 weeks[111]
Disadvantages	Improvement lasts for about 3 weeks[111]	Slower onset of action than plasmapheresis (3–10 days)[28,111]
Remark	Due to loss of albumins, double filtration plasmapheresis is less commonly used than immunoadsorption plasmapheresis[111]	-

5.0 Refractory MG

There is no general consensus regarding the definition of refractory MG.[113]
Patients are **classified as treatment refractory** if they[113]:

- fail to respond adequately to conventional therapies (maximal safe dose of steroids and at least one immunosuppressant at an adequate dose and duration);
- are unable to reduce the use of immunosuppressants without clinical relapse or need for ongoing rescue therapy, such as IVIg or plasma exchange;
- are intolerant to immunosuppressants;
- have co-morbid conditions that restrict the use of conventional therapies; and
- have frequent myasthenic crises even on therapy

About 10% of MG patients are treatment refractory and **risk factors** include[113]:

- younger age at onset;
- female gender;
- anti-MuSK+ and
- presence of history of thymoma

Refractory MG causes considerable disability and frequent emergency admissions and intensive care unit hospitalizations, with systemic complications and significant increase in mortality.[114]

For patients with refractory MG, serial IVIg or plasma exchange is considered, but benefits are temporary at a high cost.[9] Instead, cyclophosphamide and new emerging therapies, such as B cell-targeting therapies and terminal complement activation inhibitors should be considered.[84,113]

5.1 B cell-targeting therapies

5.1.1 RTX

- RTX, a chimeric anti-CD20 monoclonal antibody, leads to B cell inactivation by complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity.[113]
- The standard initial treatment dosing is 375 mg/m^2 body surface area (BSA) once weekly for 4 weeks, followed by maintenance with 375 mg/m^2 BSA once every 2 months until disease progression or for a maximum period of 2 years (12 infusions in total).[115] An alternative treatment regimen of 1 g given twice with 2 weeks between infusions is also used in many studies and resulted in similar results as the standard dosing.[116]
- In a meta-analysis, 16 studies that used the induction regimen of IV rituximab 375 mg/m^2 for 4 weekly, followed by re-infusion every 6 months reported overall improved clinical status in 77% and minimal manifestations or better status in 51% of the AChR-MG patients.[117]
- Notably, the peak clinical response was observed during 5–6 months and time-to-relapse was about 4–5 months following the first infusion, suggesting a relatively rapid and durable efficacy.[117]
- Among all types of MG, RTX showed a more favourable outcome in patients with MuSK-MG.[116]
- The most frequently reported serious adverse reactions are infusion-related reactions, infections and cardiovascular events, such as arrhythmia.[115] Notably, interstitial lung disease and progressive multifocal leukoencephalopathy (PML) are rare but potentially fatal side effects.[115]

5.1.2 Other emerging monoclonal antibody therapies

- Obinutuzumab causes direct anti-CD20 cell death; its superiority to rituximab in the treatment of MG is unproven.[111]
- Belimumab is a humanized IgG1 monoclonal antibody that neutralizes B-cell activating factor.[111,116] The results from a phase 2, randomized, double-blind trial of 39 patients with MG made available recently showed that compared with placebo, belimumab was more effective in reducing QMG score after 24 weeks of treatment.[111,116]
- Tocilizumab is a humanized recombinant anti-IL-6 monoclonal antibody.[111,116] In a published case report of two patients with refractory MG after failure to respond to RTX, it has shown clinical improvement.[116]
- Inebilizumab is a monoclonal antibody that depletes CD19+ B cells, which are central to MG pathogenesis.[118] Results from a phase 3 study showed improved function and reduced disease severity with inebilizumab in patients with AChR-MG or MuSK-MG.[118]

5.2 Complement inhibitors

- Complements and MAC have been implicated in the pathophysiology of AChR-MG.[111,116] Complement inhibitors (ie, eculizumab, ravulizumab and zilucoplan) target the key immune mechanism resulting in endplate destruction and have shown encouraging results in MG (**Table 14**).[116]
- Patients with anti-MuSK autoantibodies do not respond to complement inhibitors as these autoantibodies do not activate the complement cascade.[116]

Table 14. Choices of complement inhibitors in the treatment of refractory MG[19,84,111,116,119–124]

	Eculizumab	Ravulizumab	Zilucoplan
Approval	NPRA approved (September 2024)	NPRA approved (September 2024)	Not available but approved in the United States and European Union
MOA	Humanized monoclonal antibody that acts on terminal complement protein C5[111]	Modified version of eculizumab to achieve prolonged complement inhibition that allows less frequent dosing[111]	• Small (3.5 kDa), 15-amino acid macrocyclic peptide that binds to complement protein C5 with high affinity and specificity, preventing the cleavage of C5 into complement components C5a and C5b[111,116] • Also prevents binding between C5b and C6[111,116]
Onset of action	2–4 weeks[84]	1 week[119]	1 week[120]

	Eculizumab	Ravulizumab	Zilucoplan
Effectiveness	• Significant reduction in the QMG score vs. placebo over a 4-month period[116] • The phase 3 trial of REGAIN demonstrated favourable results with eculizumab over placebo[19,111,116] – benefits were seen within 4 weeks of initiating treatment, with maximal effects observed within 12 weeks.[121] At week 26, 61% achieved improved status vs. 42% with placebo and 25% achieved minimal manifestations vs. 13% with placebo[122]	Significant improvement in the MG Activities of Daily Living (MG-ADL) total score from baseline at week 26[111]	For patients who received daily SC doses of 0.1 mg/kg or 0.3 mg/kg zilucoplan or placebo for 12 weeks, QMG score was significantly reduced with a 6-point change in the 0.3 mg/kg group[111,116]
Safety and tolerability	• Safety profile was consistent and no cases of meningococcal disease during the interim analysis period were recorded[111] • Most common side effects include headache, nasopharyngitis, URTI, diarrhoea and nausea[122]	• Safety and tolerability profile was consistent with that observed in previous phase 3 studies and with that of eculizumab[119] • Most common side effects include diarrhoea, URTI and headache[123]	• Safety and tolerability profiles were favourable and comparable with those of placebo[111,116] • Most common side effects include injection site reactions, URTI, diarrhoea, UTI and nausea[120]

	Eculizumab	Ravulizumab	Zilucoplan
Dosing schedule	Initial phase: 900 mg *via* 25–45 mins IV infusion weekly for 4 weeks Maintenance phase: 1,200 mg *via* 25–45 mins IV infusion on 5th week and subsequently, every 14 days[124]	Loading dose (IV): ≥40–<60 kg: 2,400 mg ≥60–<100 kg: 2,700 mg ≥100 kg: 3,000 mg Maintenance dose (IV) (administer 2 weeks after loading dose for every 8 weeks): ≥40–<60 kg: 3,000 mg ≥60–<100 kg: 3,300 mg ≥100 kg: 3,600 mg[121]	OD (SC injection): <56 kg: 16.6 mg ≥56–<77 kg: 23 mg ≥77 kg: 32.4 mg[116]
Remarks	• Meningococcal vaccination is required prior to treatment[116] • Eculizumab is ineffective for carriers of rare C5 mutations (ie, about 3.5% of the healthy individuals in the Japanese population)[111]	Meningococcal vaccination is required prior to treatment[121]	• Meningococcal vaccination is required prior to treatment[116] • While still in phase 3 development (RAISE), it is suggested that zilucoplan might benefit patients with refractory MG and patients who carry C5 mutations[111,116]

5.3 FcRn antagonists

- Limiting the circulation of endogenous pathogenic antibodies is another way to address the immune pathway in MG patients.[116]
- FcRn promotes IgG recycling from lysosomal degradation.[115] FcRn antagonists inhibit the binding of IgG antibodies to FcRn, which helps to accelerate the removal of autoantibodies and shorten their half-lives that consequently reduce serum IgG level.[111,116] Similar to plasma exchange, this intervention effectively reduces circulating blood IgG antibodies, including the pathogenic antibodies.[111]
- FcRn antagonists, including rozanolixizumab, nipocalimab, batoclimab, orilanolimab, bivalent antibody mimetics (eg, ABY-039) and Fc fragments (eg, efgartigimod) have been studied in the management of MG and other autoimmune diseases (**Table 15**).[111]

Table 15. Choices of FcRn antagonists in the treatment of MG[111,113,125-130]

	Rozanolixizumab	Nipocalimab	Batoclimab	Efgartigimod
MOA[113]	Humanized IgG4 anti-FcRn monoclonal antibody	Fully human deglycosylated IgG1 anti-FcRn monoclonal antibody	Human recombinant anti-FcRn monoclonal antibody	Humanized IgG1-derived Fc fragment
Effectiveness	A phase 3, randomized, double-blind and placebo-controlled trial showed clinically meaningful improvements in patient-reported and investigator-assessed outcomes in patients with generalized MG, for both 7 mg/kg and 10 mg/kg doses[125]	A phase 3 randomized double-blind and placebo-controlled trial involving patients with AChR-MG, MuSK-MG and LRP4-MG showed that nipocalimab when added to standard-of-care therapy is a safe treatment for sustained disease control over 6 months.[126] An ongoing open-label extension phase may provide longer-term sustained safety and efficacy data of nipocalimab[126]	Positive results were demonstrated by a completed RCT and a following open-label extension study (NCT03863080) in patients with generalized AChR-MG[111]	A phase 3, randomized, double-blind, placebo-controlled trial in patients with MG (77% with AChR-MG) showed that significantly more patients in the efgartigimod group were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in cycle 1 than in the placebo group ($p<0.0001$)[129]
Safety	Higher incidence of headache and diarrhoea than placebo[125]	Generally safe and well tolerated[127]	Well tolerated[128]	Well tolerated, with the most frequent adverse events being headache and nasopharyngitis in the efgartigimod and placebo groups[129]
Dosing schedule[130]	SC, 7 mg/kg weekly for 3 weeks followed by weekly 7 mg/kg or 4 mg/kg injections for 3 more doses	IV infusion of 60 mg/kg every 2 weeks	SC 340 or 680 mg every week induction, followed by maintenance of 340 mg every 1 or 2 weeks	IV, first cycle of 10 mg/kg/dose weekly for 4 weeks and repeat cycles at variable intervals based on symptom recurrence

5.4 Cyclophosphamide

- Cyclophosphamide is an alkylating agent that can suppress bone marrow cell replication and B and T cell immune system.[84]
- Cyclophosphamide can be administered as monthly 500 mg/m^2 IV pulse for 6 cycles.[84]
  - In a RCT, monthly pulsed cyclophosphamide demonstrated significant improvement in muscle strength at month 12 and significant reduction of steroid doses at months 6 and 12, compared with placebo.[131]
  - Side effects are common, including nausea and vomiting, alopecia, leukopaenia and haemorrhagic cystitis, with potential risk of teratogenicity.[84]
- Rebooting the immune system with high-dose cyclophosphamide (50 mg/kg/day for 4 days), followed by granulocyte colony-stimulating factors (G-CSF) + prophylactic antibiotics + sulfamethoxazole/trimethoprim resulted in dramatic clinical improvement for at least 5 months in 92% of patients with refractory MG (17% had durable response up to 7.5 years).[132]
- An alternative of reboot therapy, induction cyclophosphamide 0.75 g/m^2 monthly for 6 cycles followed by maintenance oral immunosuppression with mycophenolate, azathioprine or methotrexate, showed 75% of patients with refractory MG improved within 3 months of treatment and 50% remained in clinical remission (mean follow-up of 21 months).[133]
- Patients should use effective contraception during treatment and for up to 12 months after completion of treatment.[134]
- Cyclophosphamide remains an option for severe and refractory MG but poor tolerability profile and new emerging therapies make it a less favourable choice.[84]

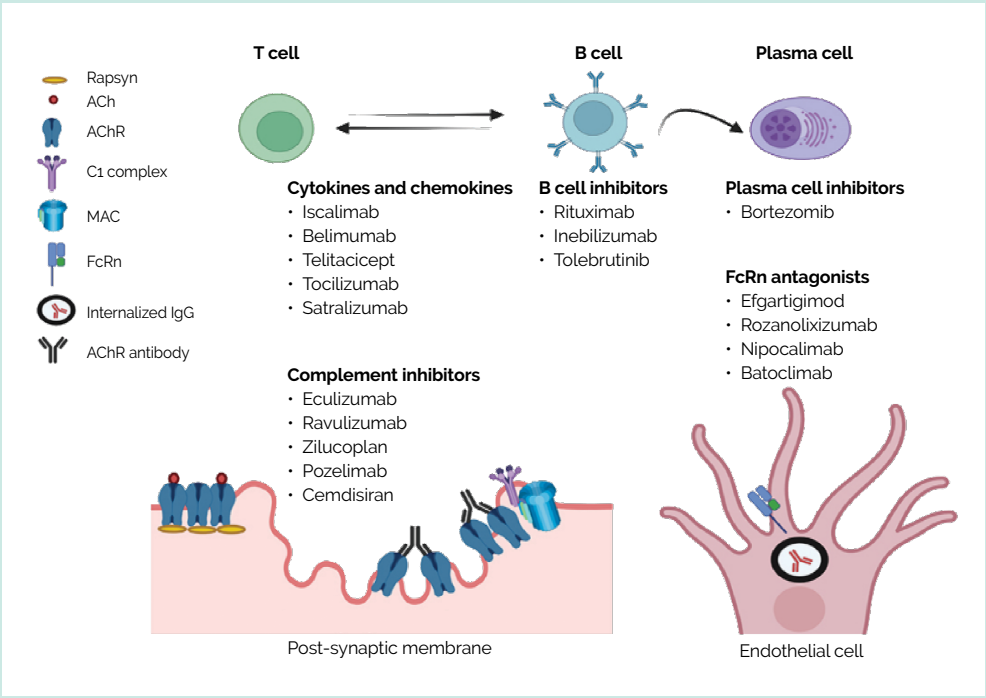
5.5 Ongoing research

Autologous haematopoietic stem cell transplantation (HSCT) is currently being investigated; case studies suggested the potential of HSCT in producing long-term remission.[1,116]

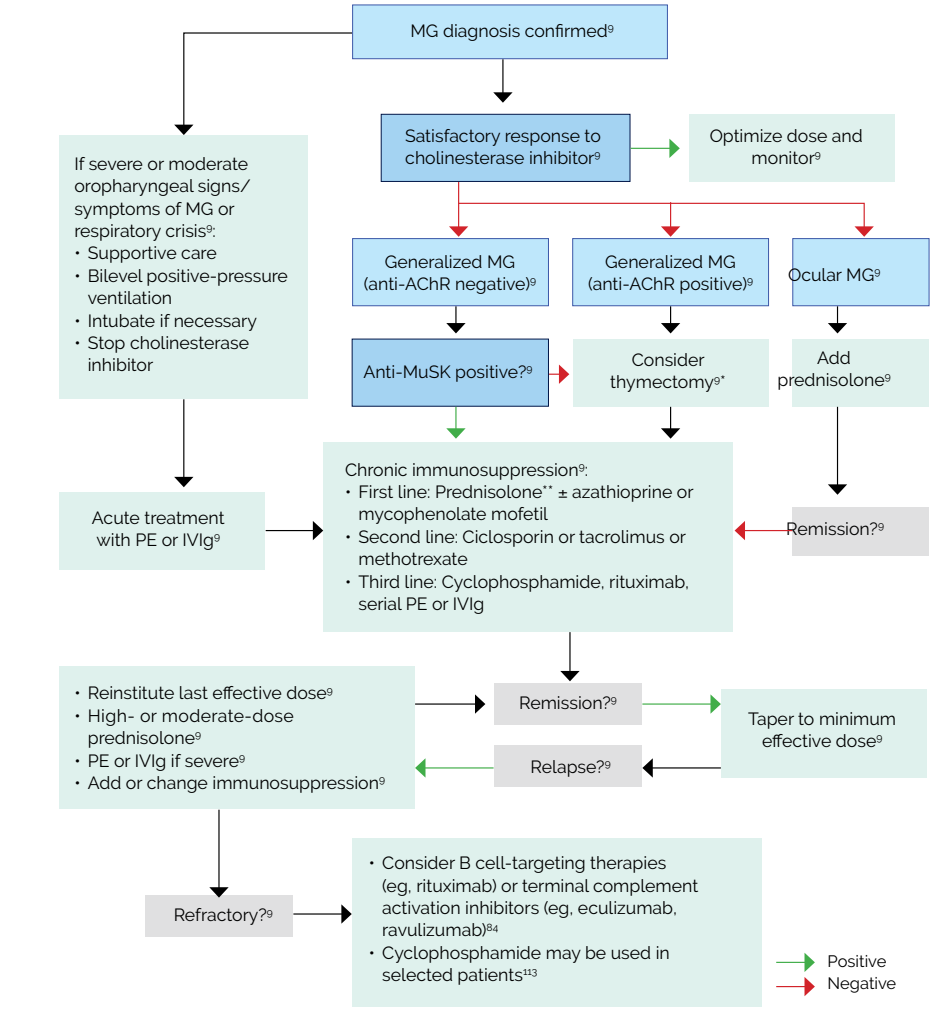
Subcutaneous gamma globulin is currently being investigated as one of the treatment options of MG in a multicentre study.[84]

Meanwhile, a recently completed phase 2 study with tirasemtiv, a drug that increases muscle contractions to improve strength in patients with MG, showed some encouraging results.[84]

Figure 8. Targets of novel therapeutic options in MG[130]



Treatment algorithm of MG[9,84,113]



Adapted from Meriggioli MN, Sanders DB 2009 and Farmakidis C, et al 2018.
*Pre-operative immunosuppression (PE or IVIg with or without steroids) might be required, particularly in patients with oropharyngeal or respiratory weakness, but some patients can successfully undergo thymectomy without prior treatment[9]
**Prednisolone can be tapered down once the patient is stable[9]
MG, myasthenia gravis; AChR, acetylcholine receptor; PE, plasmapheresis; IVIg, intravenous immunoglobulin

Treatment monitoring

Patient-reported assessment tools

MG-ADL[135]
Eight test items to assess symptoms and activities in MG

- Talking, chewing, swallowing (3 items)
- Breathing
- Impaired ability to brush teeth/to comb hair
- Impaired ability to rise from a chair
- Double vision
- Eyelid droop

- MG-ADL total score range: 0–24
  - Items measured on a 0–3-point scale (refer to Appendix 2)
- Takes 2–3 minutes to complete

MG-QOL15 or MG-QOL15r[136,137]
Fifteen test items to assess quality of life

- Mobility (9 items)
- Symptoms (3 items)
- General contentment (1 item)
- Emotional well-being (2 items)

- MG-QOL15 total score range: 0–60
  - Items measured on a 0–4-point scale (refer to Table 1 in Appendix 3)
- MG-QOL15r total score range: 0–30
  - Items measured on a 0–2-point scale (refer to Table 2 in Appendix 3)

Physician-reported assessment tools

QMG[138]
Thirteen test items to assess weakness

1. Facial muscles
2. Right arm outstretched
3. Left arm outstretched
4. Right-hand grip
5. Left-hand grip
6. Right leg outstretched
7. Left leg outstretched
8. Double vision
9. Ptosis
10. Swallowing
11. Speech
12. Vital capacity
13. Head lift

- QMG total score range: 0–39
  - Items measured on a 0–3-point scale (refer to Appendix 4)

MG Composite (MGC)[139]
Ten test items to assess signs and symptoms

Patient history
1. Talking
2. Chewing
3. Swallowing

Physician examination
4. Ptosis
5. Double vision
6. Eye closure
7. Neck flexion or extension
8. Shoulder abduction
9. Hip flexion

Other
10. Breathing

- MGC total score range: 0–50
  - Items measured using weighted response options (refer to Appendix 5)

Key highlights

- MG is an autoimmune disorder affecting the NMJ.[1]
- The cardinal feature of MG is fatigable muscle weakness, which worsens with exercise and improves with rest.[2]
- MG may occur either as a distinct primary immunological disease or as a paraneoplastic syndrome associated with thymic tumour.[24]
- The most common underlying defect in MG is a decrease of available AChRs at the NMJs due to an antibody-mediated autoimmune attack, which impairs neuromuscular transmission, leading to fatigability and muscle weakness.[24,25,27]
- MG is suspected based on characteristic clinical features and confirmed by antibody assays and/or neurophysiological tests.[37]
- Serum AChR antibody test (preferably RIPA assay) should be performed in all patients; in those with a negative test, serum MuSK antibody should be tested.[37,42] In patients with dSNMG, tests for clustered AChR and LRP4 antibodies should be considered.[1,48,49]
- RNS and/or SFEMG can be used to support diagnosis in seronegative MG, which should be performed by trained personnel.[12,37]
- Thyroid function test should be performed in all patients, in addition to thymus imaging (CT or MRI).[1,37,82]
- MRI brain and orbit should be considered especially in patients with negative serology and neurophysiological tests.[78,80]
- Cholinesterase inhibitors remain the first-line symptomatic treatment in patients with generalized and ocular MG.[9]
- Steroids should be initiated in patients with generalized or ocular MG who achieve partial response to cholinesterase inhibitors.[77]
- For patients who are steroid-dependent or experience severe side effects of corticosteroids, other steroid-sparing agents should be considered with caution of potential side effects and regular monitoring.[28]
- In patients with thymoma, thymectomy should be performed regardless of the antibody status.[9,84]
- IVIg or plasmapheresis remains the first-line treatment in patients with myasthenic crisis.[84]
- In the management of refractory MG, new emerging therapies such as B cell-targeting therapies (eg, RTX) and terminal complement activation inhibitors (eg, eculizumab) should be considered; cyclophosphamide may be used in selected patients.[84,113]

Appendix

Appendix 1

Medications that can trigger worsening of myasthenic symptoms
Corticosteroids
β-blockers
Desferrioxamine (deferoxamine)
Antibiotics (eg, aminoglycosides, macrolides and quinolones)
Chloroquine and hydroxychloroquine
Statins (eg, atorvastatin, pravastatin, rosuvastatin and simvastatin)
Telithromycin
IV magnesium
D-penicillamine
Quinine
Botulinum toxin
Immune checkpoint inhibitors (eg, pembrolizumab, nivolumab and ipilimumab)
Procainamide
Iodinated contrast media

Appendix 2

MG-ADL scoring (total score range 0–24)

Test items	Score				
	0	1	2	3	Total
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech	
1. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath (SOB) with exertion	SOB at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, sometimes uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Appendix 3

Table 1. MG-QOL15 scoring (total score range 0–60)

Please indicate how true each statement has been (over the past 4 weeks)	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
1. I am frustrated by my condition					
2. I have trouble using my eyes					
3. I have trouble eating					
4. I have limited my social activity because of my condition					
5. My condition limits my ability to enjoy hobbies and fun activities					
6. I have trouble meeting the needs of my family					
7. I have to make plans around my condition					
8. My occupational skills and job status have been negatively affected					
9. I have difficulty speaking					
10. I have trouble driving					
11. I am depressed about my condition					
12. I have trouble walking					
13. I have trouble getting around public places					
14. I feel overwhelmed by my condition					
15. I have trouble performing my grooming needs					

Total score

Table 2. MG-QOL15r scoring (total score range 0–30)

Please indicate how true each statement has been (over the past 4 weeks)	Not at all	Somewhat	Very much
	0	1	2
1. I am frustrated by my condition			
2. I have trouble using my eyes			
3. I have trouble eating			
4. I have limited my social activity because of my condition			
5. My condition limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family			
7. I have to make plans around my condition			
8. My occupational skills and job status have been negatively affected			
9. I have difficulty speaking			
10. I have trouble driving			
11. I am depressed about my condition			
12. I have trouble walking			
13. I have trouble getting around public places			
14. I feel overwhelmed by my condition			
15. I have trouble performing my grooming needs			

Total score

Appendix 4

QMG scoring (total score range 0–39)

Test items	None	Mild	Moderate	Severe
	0	1	2	3
Double vision on lateral gaze right or left (circle one)	61 secs	11–60 secs	1–10 sec(s)	Spontaneous
Ptosis (upward gaze)	61 secs	11–60 secs	1–10 sec(s)	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 secs	90–239 secs	10–89 secs	0–9 sec(s)
Left arm outstretched (90° sitting)	240 secs	90–239 secs	10–89 secs	0–9 sec(s)
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 secs	30–119 secs	1–29 sec(s)	0 sec
Right leg outstretched (45° supine)	100 secs	31–99 secs	1–30 sec(s)	0 sec
Left leg outstretched (45° supine)	100 secs	31–99 secs	1–30 sec(s)	0 sec
Total				

Appendix 5

MGC scoring (total score range 0–50)

Test items	Score			
1. Ptosis, upward gaze (physician examination)	>45 secs = 0	11–45 secs = 1	1–10 sec(s) = 2	Intermediate = 3
2. Double vision on lateral gaze, left or right (physician examination)	>45 secs =0	11–45 secs = 1	1–10 sec(s) = 3	Intermediate = 4
3. Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eyes closed) = 2
4. Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal speech, but can be understood = 4	Difficult to understand speech = 6
5. Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
6. Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing (eg, necessitating changes in diet) = 5	Gastric tube = 6
7. Breathing (thought to be caused by MG)	Normal = 0	SOB with exertion = 2	SOB at rest = 4	Ventilator dependence = 9
8. Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (ie, ~50% weak, ±15%) = 3	Severe weakness = 4
9. Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (ie, ~50% weak, ±15%) = 4	Severe weakness = 5
10. Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (ie, ~50% weak, ±15%) = 4	Severe weakness = 5
Total				

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