

Myasthenia gravis and immunoglobulin therapy

CLINICAL GUIDANCE ARTICLE



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This clinical guidance article has been developed as a part of the *Value in Prescribing – Immunoglobulins products* program. The program represents an evidence-based approach to fostering responsible stewardship of immunoglobulin (Ig) products and ensuring the viable and sustainable supply of Ig products in accordance with the National Policy, including the [Criteria for the clinical use of immunoglobulin in Australia](#).

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Abbreviations

Ab: antibodies

AChE: acetylcholinesterase

AChR: acetylcholine receptor

Agreement: National Blood Agreement

AZA: azathioprine

BloodSTAR: Blood System for Tracking Authorisations and Reviews

BMI: body mass index

CMS: congenital myasthenic syndromes

COVID-19: coronavirus disease 2019

CPEO: chronic progressive external ophthalmoplegia

Criteria: Criteria for the Clinical use of Immunoglobulin in Australia

GBS: Guillain-Barré syndrome

IBW: ideal body weight

Ig: immunoglobulin

IVIg: intravenous Ig

LEMS: Lambert-Eaton myasthenic syndrome

LifeBlood: Australian Red Cross, Lifeblood

LMN: lower motor neuron

MG: myasthenia gravis

MG-ADL: myasthenia gravis activities of daily living

MGC: myasthenia gravis composite score

MGI: myasthenia gravis impairment index

MMF: mycophenolate

MMS: myasthenia muscle score

MRA: magnetic resonance angiography

MSAC: Medical Services Advisory Committee

MSS: myasthenia severity scale

MTX: methotrexate

MuSK: muscle-specific tyrosine kinase

MuSK-Ab: muscle-specific tyrosine kinase antibody

MuSK-LRP4: muscle-specific tyrosine kinase antibody–lipoprotein receptor-related protein

NBA: National Blood Authority

OPDM: oculopharyngeal distal myopathy

OPMD: oculopharyngeal muscular dystrophy

PLEX: plasma exchange

QMGS: quantitative myasthenia gravis score

RNS: repetitive nerve stimulation

RTX: rituximab

SCIg: subcutaneous Ig

SFEMG: single fibre electromyography

TGA: Therapeutic Goods Administration

TBW: total body weight

UMN: upper motor neuron

Overview

Key points

- ▶ In myasthenic crisis, intravenous immunoglobulin infusion has non-inferior effectiveness and superior safety compared with plasma exchange in small studies. Acute treatment with intravenous immunoglobulin (IVIg) is indicated in severe, generalised myasthenia gravis (MG) affecting respiratory and/or bulbar muscles.
- ▶ IVIg infusion prior to surgery and/or thymectomy is indicated for patients with advanced MG, bulbar symptoms and/or respiratory involvement.
- ▶ As an adjunct treatment in chronic MG, IVIg should be a stop-gap treatment whilst the patient stabilises on other standard therapies. IVIg does not result in disease remission.

Background

Myasthenia gravis (MG) is a rare autoimmune disorder affecting neuromuscular transmission. The name is an amalgam of Greek and Latin, and literally translates to 'severe muscle weakness'. The characteristic feature of MG is variable weakness affecting one or more of the ocular, bulbar, limb and axial/respiratory muscles. Once a frequently fatal disease akin to motor neuron disease, MG is now considered to be a very treatable disease, with hospitalised mortality rates around 2%.¹

Epidemiology

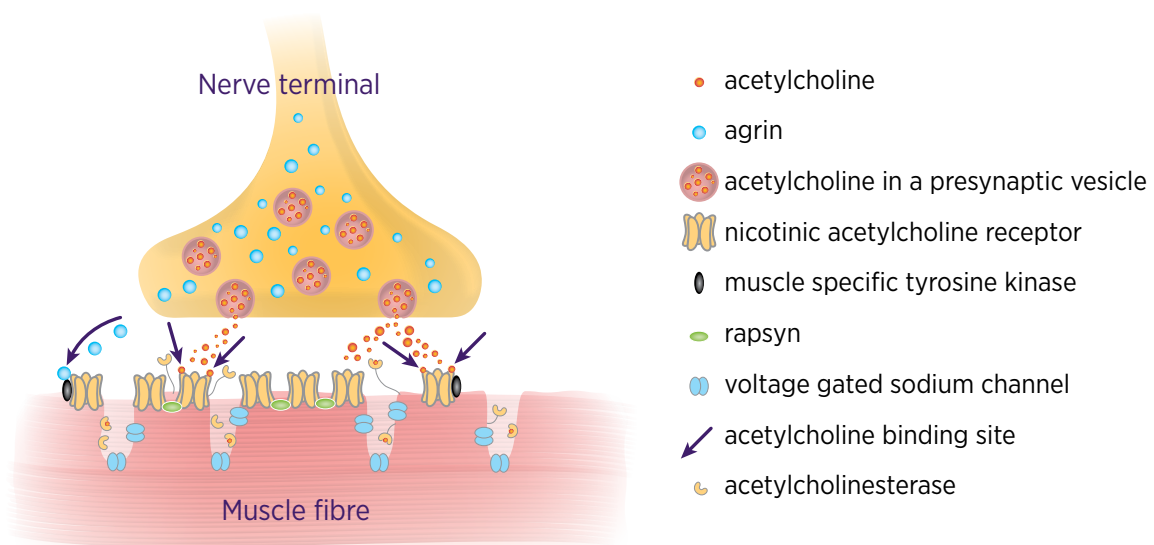
Published incidence and prevalence rates of MG show marked variation worldwide. Australia has one of the highest reported incidences of MG at 24.9 per million person years with a prevalence of 117.1 per million.² There is a bimodal distribution in regard to age of onset, with an initial peak predominantly affecting females around the 3rd decade, with a later peak accounting for most affected males in the 6th to 8th decades.³ This late male peak is not commonly seen in autoimmunity. A number of genetic and environmental factors have been implicated as risk factors for the development of MG.⁴

Pathogenesis

Acquired MG is considered the archetypal model of an autoimmune channelopathy. It is caused by the production of autoantibodies against post-synaptic membrane proteins at the neuromuscular junction.

Neuromuscular junction signalling relies on the release of acetylcholine from pre-synaptic nerve terminal vesicles in response to an influx of calcium ions triggered by a motor nerve action potential (Figure 1). Acetylcholine binds and opens the post-synaptic acetylcholine receptor (AChR) resulting in cation influx (sodium, calcium ions) and membrane depolarisation. This in turn activates voltage-gated sodium channels, generating a muscle action potential which ultimately results in muscle contraction.

The structure of the post-synaptic membrane is critical for effective neuromuscular transmission. The post-synaptic membrane forms folds containing high-density clusters of AChR on the surface closest to the pre-synaptic surface. The alignment of AChR clusters in close proximity to the pre-synaptic membrane is crucial for acetylcholine signalling. Clustering of AChR is a requirement for acetylcholine signalling and is dependent on the function of other post-synaptic membrane proteins including agrin, Lrp4, MuSK and rapsyn (Figure 1).^{5,6}

Figure 1: The neuromuscular junction⁷

Acetylcholine signalling at the neuromuscular junction is tightly regulated. Acetylcholinesterase located on the post-synaptic membrane directly hydrolyses acetylcholine, effectively downregulating signalling. The actions of acetylcholine are also downregulated by the disassembly or endocytosis of AChR clusters. This primarily occurs via calpain, a member of the calcium-dependent cytosolic cysteine proteinase family.^{8,9} Calpain is activated by calcium influx through open AChR, therefore the AChR receptor is downregulated by ACh release and persistence. The action of the agrin binding to Lrp4 and activating the MuSK/rapsyn pathway directly opposes the action of calpain via the sequestration of calpain by rapsyn.¹⁰ A healthy neuromuscular junction therefore relies on a balance between AChR clustering and disassembly.

Mechanism of impairment in MG

In MG, AChR antibodies impair neuromuscular transmission via a number of mechanisms:

1. Crosslinking of AChRs leading to accelerated AChR internalisation and degradation.
2. Complement-mediated lysis of the postsynaptic membrane with loss of AChR-associated proteins and post-synaptic membrane folds; and
3. Functional AChR blockade.⁵ As described above, Lrp4 and MuSK play an important role in the organisation and clustering of AChR at the motor endplate.

In mouse models, MuSK antibodies cause disassembly of AChR clusters and a reduction in acetylcholine signalling.^{11,12,13} Complement activation does not seem to be necessary for the pathogenesis of MuSK antibodies. This may reflect the fact that MuSK antibodies are mainly of the IgG4 subtype, which do not typically trigger the complement cascade.

The majority of patients with MG with AChR antibodies have abnormal thymus pathology.¹⁴ Approximately 10% of patients are found to have a thymoma, with many younger patients having thymic hyperplasia with germinal centres.¹³ Interestingly, patients with MuSK antibody-positive MG do not seem to have similar abnormal thymic pathology, but rare cases of thymoma have been identified.^{15,16} It has been hypothesised that immunomodulatory mechanisms are dysregulated in the thymus of patients with thymic hyperplasia.¹⁷

Clinical features

MG most frequently affects the ocular muscles, resulting in variable diplopia and/or ptosis. Disease purely affecting ocular muscles is referred to as ocular MG. Weakness involving bulbar, axial or limb muscles, with or without ocular muscle involvement, is referred to as generalised MG. The common symptoms of MG are listed in Table 1.

Table 1: Common symptoms in MG

Symptom	Symptom
Ocular	Axial muscles
Diplopia	Neck weakness/head drop
Ptosis (often asymmetric)	Breathlessness
Bulbar	Orthopnoea
Dysarthria	Limb muscles
Dysphonia	Painless muscle weakness
Dysphagia	Muscle fatigue
Stridor	
Facial weakness	
Weakness of masticatory muscles	

Ptosis and extraocular eye muscle weakness are often asymmetrical early in MG but may become bilateral as the disease progresses. Limb weakness is typically symmetrical and proximal. Reports of muscle fatigue without objective weakness should alert clinicians to an alternative diagnosis, such as chronic fatigue syndrome. Patients with MuSK antibody-positive MG classically present with marked bulbar and respiratory weakness,¹⁸ with tongue and facial muscle atrophy not uncommon but primary ocular presentations also occur.¹⁹ Patients with MuSK antibody-positive MG are at particular risk of respiratory crises requiring ventilator support.¹⁸ Lambert-Eaton myasthenic syndrome (LEMS) should be considered if lower limb weakness predominates, often in association with autonomic symptoms such as a dry mouth, constipation and erectile dysfunction.

Patients may present to non-neurologists with symptoms due to MG. These include patients with exertional dyspnoea, dysphonia, visual motility disorders, and weakness or paralysis after neuromuscular blocking anaesthetics or aminoglycosides.

Clinical course

Approximately 50% of patients diagnosed with MG will present with isolated ocular symptoms.²⁰ More than half of these patients, particularly those with AChR antibodies versus seronegative patients, will go on to develop generalised disease within 2 years.²¹

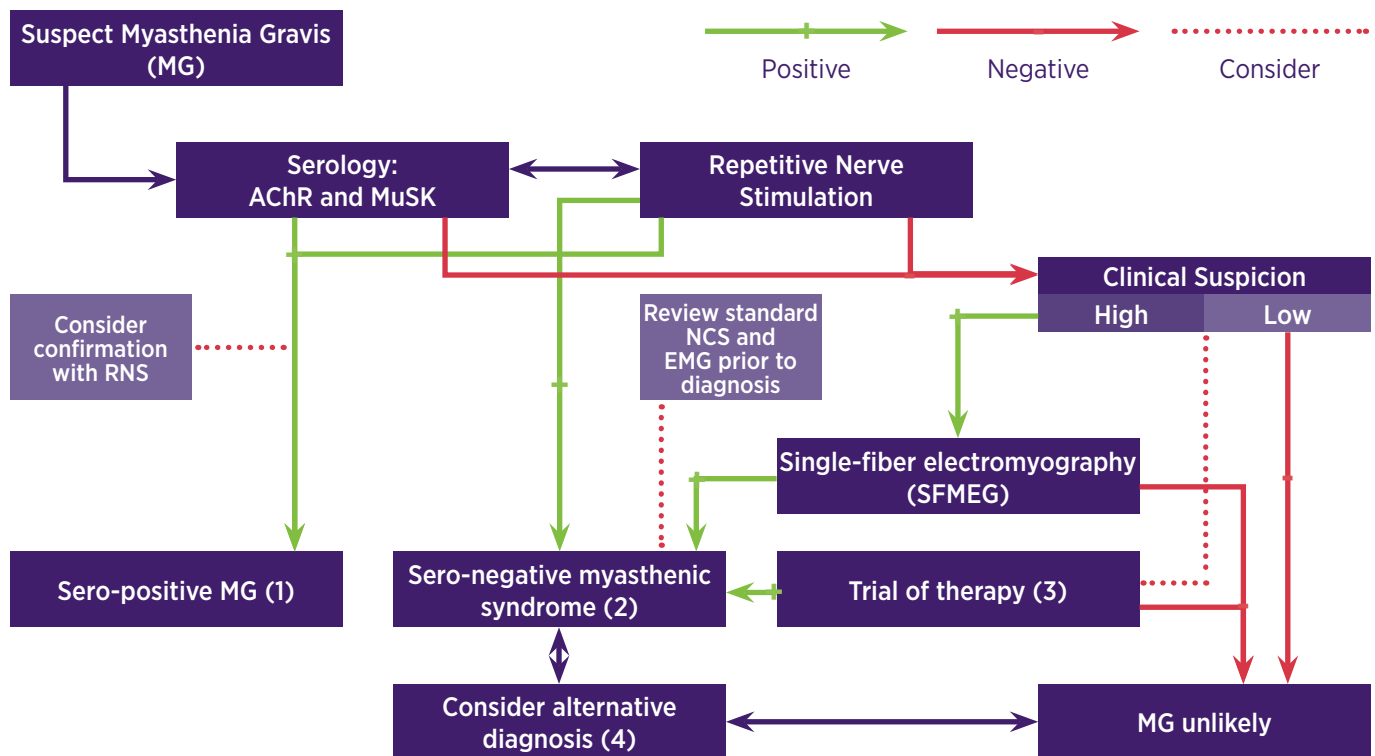
Symptoms in MG typically develop over days to weeks, although occasionally patients will describe a more acute onset, and some may have had intermittent symptoms for years. Symptoms are often minimal or absent on first waking, with progressive worsening as the day progresses. Symptoms are exacerbated with exertion or repetitive use of affected muscles, or with increased body temperature. It should be noted however that all ptosis worsens later in the day, including normal tired eyes, whereas myasthenic ptosis evolves over minutes.

Diagnosis and misdiagnosis of MG

Diagnosing MG can be straightforward when patients present with objective fatigable weakness supported by confirmatory antibody tests, electrophysiology, or pharmacological tests. These tests are complementary and may confirm the autoimmune nature of the disease (antibodies), define the pathophysiology as unstable neuromuscular transmission (repetitive nerve stimulation [RNS], single fibre electromyography [SFEMG]), or confirm benefit from cholinergic stimulation (Tensilon test). These tests are more likely to be positive in subjects with generalised disease compared with localised (eg, ocular) presentations (Figure 2). The challenges arise when a history of weakness is accompanied by an inconclusive examination, negative serological tests, and normal neurophysiology. While it is important to consider MG in the differential diagnosis of fatigable weakness, the diagnosis should only be made when clearly supported by clinical findings and appropriate investigations. Table 2 lists features on history and examination that should act as red flags, prompting clinicians to look for an alternative diagnosis to autoimmune MG.

Diagnostic tests

A testing algorithm can be found in Figure 2.

Figure 2: Diagnostic testing algorithm for MG

- (1) Clinical suspicion with positive antibodies by radioimmunoassay generally establishes autoimmune myasthenia gravis, consider confirmation with electrophysiology. Enzyme-linked immunoassay (EIA, ELISA) detection of antibodies is more prone to false positive results.
- (2) Clinical suspicion with electrophysiological confirmation but negative antibodies may include sero-negative myasthenia gravis, Lambert Eaton myasthenia syndrome, congenital myasthenia syndrome, other neuromuscular disease. SFMEG is regularly abnormal and RNS is occasional abnormal in other neuromuscular disease. Electrophysiological studies may also be false positively abnormal due to technical factors or inexperience combined with non-neuromuscular disorders, as a general rule consider repetition of any potentially discordant test.
- (3) Includes cholinesterase (Tensilon test), corticosteroids and plasma exchange (in rare circumstances when differentiating congenital MG).
- (4) Exclude neuropathy, MND, myopathy causing false positives.

Ab = antibodies; AChR = acetylcholine receptor; EMG = electromyography; MG = Myasthenia gravis; MND = motor neurone disease; MuSK = muscle-specific tyrosine kinase; NCS = nerve conduction studies; RNS = repetitive nerve stimulation; SFMEG = single fibre electromyography

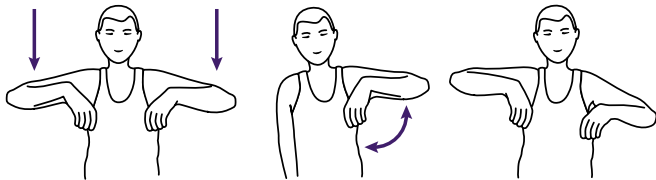
Clinical tests

Ice pack test

In patients presenting with ptosis, the ice pack test can be a useful bedside diagnostic tool for MG. Easy, quick and safe, the test requires an ice pack or ice-filled balloon/glove to be applied to the ptosed lid for approximately 2 minutes. Cooling the levator muscle improves neuromuscular function, conversely ptosis worsens with a warm pack.²² A positive test is defined as an improvement in the ptosis (measured at the palpebral fissure) by at least 2 mm. Before and after photos can be helpful in determining whether the test is positive.

The ice pack test has a reported sensitivity and specificity for MG of over 92% and 98% respectively.²³ However, false positives can occur in patients with blepharospasm or other conditions affecting eye closure tests (authors own observations); Miller Fisher variant of Guillain-Barré syndrome (GBS);²⁴ and ptosis due to botulinum toxin type A treatment.²⁵ The ice pack test is less effective in patients with complete ptosis, which likely represents a failure of cooling to overcome severely impaired neuromuscular transmission.²⁶ The ice pack test is not reliable for other clinical manifestations of MG, including diplopia.

Figure 3: Half a chicken test



Asymmetric fatigue (half a chicken) test

MG is a condition producing both persistent weakness and short-term fatigue following muscular effort. This can be evaluated readily by simultaneously examining bilateral shoulder abduction strength at 90° then asking the patient to 'flap' the arm at the shoulder for 30 repetitions before retesting bilateral strength for newly developed asymmetrical weakness in

the exercised arm (Figure 3). Elbow flexion or hip flexion can be tested in the context of other arm or shoulder issues. This clinical test has not been formally evaluated against standard tests.

Tensilon test

The edrophonium (Tensilon) test is a somewhat outdated bedside therapeutic test of documented improvement after administration. It is most useful in patients with quantifiable muscle weakness, particularly ptosis or extraocular muscle weakness. Improvement should be objective and documented. Edrophonium potentiates both muscarinic and nicotinic acetylcholine (acetylcholinesterase [AChE] inhibitor) signalling; therefore, it is contraindicated in patients with a history of cardiac disease or asthma. Monitoring, atropine and resuscitation equipment should be available.

The Tensilon test is most useful in subjects with ocular MG, especially since this group where serology and RNS are less sensitive. In ocular MG, sensitivity is around 92% (compared with 82% in generalised MG); specificity is similar in both groups of patients (97%).²⁷ False-positive results have been described in a number of other diseases, including LEMS, botulism, GBS and brainstem glioma.^{28,29,30,31} In practice, it is more often confounded than the specificity would suggest, with additional positive responses in patients with dynamic eye movement disorders and nebulous or functional issues. Neostigmine with a longer duration of action can be used, with the same caveats, given limited availability of edrophonium.

Serological tests

Once there is a clinical suspicion of MG, patients should undergo serological testing for the presence of AChR and MuSK antibodies.

Patients with MG are sub-grouped based on the presence of these antibodies (as well as their clinical phenotypes, thymus pathology, and age at onset). AChR antibodies are detected in 80% to 90% of patients with generalised MG and 50% of patients with ocular MG, with 99% specificity in both cases.²⁷ Up to 15% of patients who are seronegative for AChR antibodies on initial testing will have AChR antibodies detected on subsequent tests. In established patients with MG who are AChR antibody negative, about 50% will have MuSK antibodies.¹⁸

An estimated 10% of patients are referred to as 'seronegative', however it is possible they may have antibodies to AChR or MuSK that are not detectable using currently available commercial assays, although they may use cell based assays. Alternatively, these patients may have rarely identified antibodies to other endplate proteins such as Lrp4 or agrin, or have related conditions such as LEMS or congenital myasthenic syndromes (CMS).

False positives to either test are very rare using radioimmunoassay, but are occasionally seen in non-myasthenic patients with thymoma. Some of these patients will later develop MG. Enzyme linked immunosorbent assay (EIA, ELISA) for AChR antibodies is more prone to false-positive results.³²

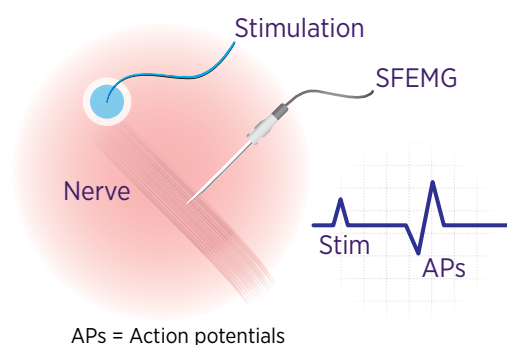
Electrophysiology assessment

RNS is a diagnostic technique recording the muscle response to a short series of electrical pulses. For best results this should be performed in clinically weak muscles, or at least involve testing of both proximal and distal muscles, however not all relevant muscles are technically accessible.³³

Abnormal RNS comprises a reproducible, smooth and artefact-free reduction in the compound muscle action potential amplitude of at least 10% at low stimulation frequencies of 2–3 Hz. These tests are superficially simple but require meticulous attention to technical factors to avoid misinterpretation. Irregular fluctuation in waveforms due to shift of the stimulator, change in position of the electrodes due to poor immobilisation, and failure to use supramaximal stimulation may all result in the false impression of decrement. In true decrement, the largest proportional amplitude drop is seen between the first and second pulse, and the lowest minimal response usually occurs between pulse four and six. A short (30–60") period of isometric maximal muscle contraction may unmask decrement after 2–5 minutes delay.

In many cases, it is more efficient to test a greater number of nerve:muscle pairs rather than perform prolonged testing over 5 minutes on one muscle.³⁴ RNS is more easily performed from hand muscles (abductor digiti minimi, abductor pollicis brevis) but can readily be performed from forearm (anconeus), shoulder (trapezius, deltoid, biceps), or facial (nasalis, frontalis, orbicularis oris) muscles. The yield is often better from proximal muscles, especially if these are symptomatic.³⁴ The sensitivity is approximately 53–89% in generalised MG, but 20–60% in pure ocular disease. It is an even better test for LEMS at 97% sensitivity and is also present in most genetic myasthenias.³⁵ False positives may occur in other neuromuscular disorders including motor neurone disease and periodic paralysis.

Figure 4: 'Jitter' diagram



If RNS is negative or equivocal, and no other nerve or muscle disorder is present on detailed investigation including nerve conduction studies and electromyography, then SFEMG is recommended. SFEMG measures the time-variability between potentials recorded from individual myofibres, recognised as belonging to the same motor unit, due to their near-synchronous firing pattern. This so-called 'jitter' is measured using a fine concentric EMG needle, with the position delicately adjusted to maximise recording from related fibres with voluntary or stimulated activation. Considerable skill is required to perform and interpret these studies.³⁶

Increased jitter is seen in MG, LEMS and genetic myasthenias but is also abnormal in motor neurone disease, most active motor neuropathies and some myopathies, especially mitochondrial myopathy. Hence, SFEMG is only performed after detailed negative testing for other nerve and muscle disorders. It is important to understand that abnormal SFEMG indicates a *neuromuscular disorder*, but not *which* neuromuscular disorder, and is not at all specific for MG, nor should specificity be stated or implied in the report. It is however highly sensitive, at up to 99%, so if a weak muscle is found to have a normal SFEMG then MG is highly unlikely.³⁶

Chest imaging

All adult patients diagnosed with autoimmune MG should be assessed for the presence of a thymoma. Computed tomography (CT) of the chest is the standard imaging modality, however magnetic resonance imaging (MRI) may be a technically less satisfactory alternative when radiation exposure is a concern. In patients with severe MG symptoms, consideration should be given to avoiding intravenous iodinated contrast given the potential to worsen MG symptoms.³⁷

Other investigations

If there is any uncertainty about the diagnosis of MG, or if there are inconsistencies in clinical presentation, further investigations should be considered based on the patient's clinical history and examination (see Table 2).

Table 2: Red flags against the diagnosis of autoimmune MG

General	General
Positive family history	Bulbar
Predominant mental fatigue or tiredness	Altered conscious state
Weight loss	Pseudobulbar speech
Fever	Non-motor cranial neuropathies
Autonomic symptoms (urinary retention, constipation, erectile dysfunction, dry mucous membranes) – may suggest LEMS	Tongue fasciculations or wasting (can occur in MuSK)
Ocular	Limb and/or axial muscle weakness
Impaired visual acuity	Myalgias
Pupillary abnormalities	Muscle wasting/fasciculations
Chemosis and/or proptosis	UMN signs
Severe ocular pain/headache	Hyporeflexia (present in LEMS)
Altered facial sensation	Sensory symptoms/signs

LEMS = Lambert-Eaton myasthenic syndrome; MuSK = muscle-specific tyrosine kinase; UMN = upper motor neuron

Oculobulbar symptoms are frequently investigated with MRI of the brain and orbits (+/- magnetic resonance angiography [MRA]). Similarly, the finding of upper motor neuron (UMN) signs warrants MRI imaging of the central nervous system and would not be found in isolated MG. Inflammatory markers and creatinine kinase should be tested if myopathy is a diagnostic possibility. Lactate and pyruvate can be useful initial tests when there is a suspicion of mitochondrial disorders. Nerve conduction studies and EMG can help diagnose peripheral neuropathies, myopathy or motor neurone disease.

Patients with MG have an increased risk of other autoimmune diseases. This association is strongest in female, AChR seropositive patients. Frequent associations include autoimmune thyroid disease followed by rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, pernicious anaemia, alopecia and vitiligo, to name a few.³⁸ Inflammatory central nervous system diseases have also been implicated, with reports of multiple sclerosis and neuromyelitis optica occurring in patients with MG.³⁹ Yearly monitoring of thyroid function and vitamin B12 is suggested.

The differential diagnosis of MG is largely dependent on symptomatology and clinical signs (Table 3). Associated features can provide clues to the underlying disease process. A family history or symptoms extending back into early childhood is less common in autoimmune MG and may suggest a congenital myasthenic syndrome, however a childhood, mainly ocular, low AChR antibody positive subgroup occurs in East Asians.⁴⁰

Table 3: The differential diagnosis of MG

Differential diagnosis of MG	Clues on history and examination
Ocular (ptosis and/or diplopia)	
Thyroid orbitopathy	Chemosis, proptosis, systemic symptoms of thyroid dysfunction
Horner's syndrome	Miosis, anhidrosis, minimal fluctuation, no diplopia
Third nerve palsy	Pupillary involvement, ocular pain
Myotonic dystrophy	Cataracts, characteristics facies, intellectual impairment, cardiac conduction abnormalities, family history (autosomal dominant)
Mitochondrial cytopathies eg, CPEO	Slowly progressive bilateral symmetrical ptosis, slowed saccades, family history, minimal fluctuation in symptoms
OPMD, OPDM	Family history, autosomal dominant (OPMD) or recessive (OPDM)
Levator dehiscence	Extremely common: elevated/absent lid crease, recent ocular surgery, no diplopia, minimal fluctuation
GBS variant (eg, Miller Fisher syndrome)	Acute or sub-acute, areflexia, sensory ataxia, viral prodrome
Blepharospasm	Excessive blinking, ocular irritation, elevation of lower lid and/or depressed eyebrow, associated lower face/jaw dystonia, geste antagoniste with more extensive dystonia

Differential diagnosis of MG	Clues on history and examination
Bulbar weakness	
Motor neurone disease	Fasciculations (including tongue), mixed UMN and LMN signs, weight loss
Brainstem pathology (eg, stroke, tumour, inflammation, demyelination, infection)	Multiple cranial nerve signs, often asymmetrical symptoms, UMN signs, minimal fluctuation
GBS variants (eg, pharyngeal-cervical-brachial variant)	Viral prodrome, minimal fluctuation, associated upper limb hyporeflexia
Inflammatory myopathies (eg, polymyositis, dermatomyositis)	Myalgia, muscle atrophy, characteristic skin changes
Botulism	Descending paralysis, fixed dilated pupils, urinary retention and constipation from smooth muscle paralysis
Limb and/or axial muscle weakness	
Acquired myopathies (eg, inflammatory, drug/toxin-induced, endocrine-associated)	Myalgia, muscle atrophy, myotoxic drug use (eg, statin, colchicine, corticosteroids, alcohol), history of thyroid or Cushing's disease
Adult-onset muscular dystrophy (eg, limb girdle dystrophy)	Family history, slowly progressive, distinct patterns of weakness, little fluctuation, cardiac involvement, myalgias
Acquired neuropathy (eg, GBS/chronic inflammatory demyelinating polyradiculoneuropathy)	Often ascending paralysis, associated sensory symptoms/signs, hyporeflexia, infective or vaccination prodrome
Motor neurone disease	Fasciculations (including tongue), marked muscle wasting, mixed UMN and LMN signs, weight loss
LEMS	Onset typically hip girdle weakness, reduced/absent reflexes that increase with facilitation, associated autonomic symptoms, less prominent oculobulbar symptoms, associated malignancy (often small cell lung carcinoma)
Chronic fatigue syndrome/asthenia	Generalised fatigue with mental tiredness, no objective weakness or other abnormal neurological signs, viral prodrome, frequent history of chronic pain syndromes / fibromyalgia and co-morbid psychiatric disease

CPEO = chronic progressive external ophthalmoplegia; GBS = Guillain-Barré syndrome; OPDM = oculopharyngeal muscular dystrophy; OPMD = oculopharyngeal muscular dystrophy; LEMS = Lambert-Eaton myasthenic syndrome; LMN = lower motor neuron; UMN = upper motor neuron

The presence of features listed in Table 3 should prompt consideration of an alternative diagnosis.

Trials of therapy

In some cases of diagnostic doubt where the confirmatory testing is negative or equivocal, there may be a role for trials of treatment, but these need to be carefully monitored with objective outcome measures to ensure that a genuine response is obtained.

The ice pack test and Tensilon test are clinician-reported 'bedside' trials of therapy. A trial of pyridostigmine may confirm a cholinergic deficit at the neuromuscular junction. A trial of oral corticosteroid may be required for ocular features (with appropriate monitoring and awareness of corticosteroid toxicity and the potential false-positive mood benefits of corticosteroids). In the rare circumstance where there is question of an acquired seronegative antibody mediated MG versus a genetic, non-autoimmune MG already proven with abnormal electrophysiology, a trial of plasma exchange (PLEX) may be helpful. A trial of IVIg without a robust positive antibody or electrophysiology test for MG is not appropriate.

Treatment of MG

Overview

Individual initial and long-term treatment of MG differs based on a range of factors, including serological status, illness severity, age, sex, co-morbidities, cost and availability of treatments. The treatment goals are to minimise the risk of patients developing life-threatening bulbar or respiratory muscle weakness, to reduce the severity of the MG-associated symptoms and to restore functional capacity and quality of life. Only small numbers of patients with generalised MG will remit spontaneously. Most patients with generalised MG and at least moderate symptoms will require long-term immunosuppressant treatment to achieve reasonable control of disease, whereas patients with mild symptoms or purely ocular MG may receive adequate symptomatic benefit from AChE inhibitors alone. Treatment regimens are often complex and frequently combine a number of modalities, including:⁴¹

- ▶ symptomatic treatment via inhibition of acetylcholine breakdown with AChE inhibitors (eg, pyridostigmine), rarely 3,4-diaminopyridine, salbutamol or ephedrine
- ▶ primary immunosuppression (corticosteroids)
- ▶ corticosteroid-sparing immunosuppressants (eg, azathioprine [AZA], mycophenolate [MMF], methotrexate, rituximab, cyclophosphamide)
- ▶ immunomodulatory therapy such as IVIg and PLEX; and
- ▶ surgery (thymectomy).

Because of the vastly different modes of actions and speed of onset of the different treatments, for most patients multi-agent therapy is employed. In general, many treatment regimens are based on expert opinion and physician experience, with only few well-conducted randomised controlled trials and a number of unfortunately negative trials.

Frank discussion of risk and potential side effects of therapeutic options is warranted prior to commencement of therapy, in particular in regard to immunosuppressive side effects in general and the specific risk profile of individual agents (see Table 4). This needs to be balanced with the morbidity and mortality associated with uncontrolled MG. Managing and mitigating the side effects of immunosuppression is important for the best benefit:risk of these treatments and should be an automatic part of routine care.⁴² Evaluating potential patient-specific risks should be performed systematically and include coverage of:

- ▶ cardiovascular risks, which are worsened by both disease and treatments
- ▶ infections, which in some cases such as tuberculosis or hepatitis B may require additional therapies
- ▶ Vaccination status, including partially preventable infections such as influenza
- ▶ cancer risk, which is increased by immunosuppression, especially long term⁴³
- ▶ fertility and breastfeeding, which may impact on treatment choice and sequencing
- ▶ drug-specific issues, including corticosteroid risks.

Escalating approach to treatment

Therapeutic decisions, especially in severe MG, need to take into consideration both short-term and long-term aspects of management. During acute severe exacerbations a combination of AChE inhibitors, corticosteroids and IVIg/PLEX is commonly used. These agents work quickly (within days to weeks, slower for corticosteroids) and are highly useful in an inpatient setting. After initial stabilisation of the patient, long-term safety considerations, such as minimisation of corticosteroid doses, become more relevant. For these patients, early introduction of corticosteroid-sparing agents, as well as consideration of a referral for thymectomy should be considered, recognising that it will often take more than 1 year for these therapeutic decisions to become meaningful. As these long-term interventions become more effective, IVIg can be weaned and/or ceased, together with careful reduction of corticosteroid dose. In severe cases, third-line remission induction agents such as cyclophosphamide or rituximab may be considered.

Most patients with generalised MG and at least moderate symptoms will require long-term immunosuppressant treatment to achieve reasonable control of the disease.⁴¹ In contrast, some patients with mild symptoms or purely ocular MG only require AChE inhibitors. However, more severe cases will require an escalation in therapies, while others will need trials of therapies.⁴²

Symptomatic therapy

Pyridostigmine is commonly used as an initial symptomatic therapy in MG. It can provide temporary symptom improvement but will not affect the underlying disease process or long-term prognosis. It is rarely sufficient to solely control disease manifestations long term, and in excess may produce worsening weakness due to cholinergic crisis. Pyridostigmine may worsen MuSK MG due to the potential to impair neuromuscular junction signalling.¹² Pyridostigmine has no known long-term side effects. It is frequently continued at divided doses between 60 and 360 mg daily for most patients, with additional doses taken on a PRN (as needed) basis. Dose escalation is often limited by side effects including gastrointestinal cramping, diarrhoea, and muscle cramps.

Thymectomy

In non-thymomatous MS, thymectomy is now widely recommended for patients with generalised MG with AChR antibodies following a randomised controlled trial.⁴⁴ This showed substantially reduced prednisolone requirements if allocated to thymectomy. A post-hoc analysis has also shown that more patients achieved sustained minimal manifestations of MG off prednisone, which is functional remission, if allocated to thymectomy (64%) than if allocated to prednisone alone (38%), and more patients in the latter group also required steroid-sparing immunosuppressives.⁴⁵ Patients should ideally be early in the disease course and have good control of MG prior to operation. In the presence of significant bulbar or respiratory weakness, pre-operative treatment with IVIg or PLEX may be indicated.

Minimally invasive thymectomy techniques, in particular robotic thymectomy which permits minimally invasive full resection with adequate visualisation of the phrenic nerves, are generating interest as an alternative to more conventional trans-sternal approaches. Randomised control trials comparing the techniques are lacking, however current evidence suggests that minimally invasive thymectomy is associated with reduced hospitalisation time, improved patient satisfaction and equivalent post-operative mortality and complete stable remission rates.³²

In MG patients with thymoma, thymectomy is indicated, given the potential to compress or invade neighbouring structures, including the pericardium, lung and great vessels. Paradoxically, removal of the thymoma rarely improves MG symptoms, and in some circumstances can be associated with clinical deterioration.⁴⁶

Oral immunotherapy

For most patients, immunotherapeutic agents are required to obtain disease control. To minimise associated toxicity, and take benefit of the different speeds of onset of the medicines used, a combination therapy is frequently started shortly after diagnosis. Doses are subsequently adjusted to optimise efficacy and minimise side effects long term.

Corticosteroids

Corticosteroids remain one of the most important treatments in MG. Cushingoid side effects limit their long-term use, especially at higher doses. Because of their relative fast speed of onset, corticosteroids are widely used. As initial deterioration of MG symptoms can be encountered if high doses of corticosteroids are started or stopped suddenly, progressive dose escalation and de-escalation is performed. A typical initiation protocol is 5-10 mg prednisolone daily, increasing by a similar amount weekly to 0.25 mg/kg (ocular) or 0.25-1 mg/kg (generalised), depending on initial severity and the capacity to cover any initial dip. A switch to alternate-day corticosteroids (the same average dose but 2x/0x on alternate days) is often made later to minimise metabolic corticosteroid effects.

Corticosteroid-sparing immunosuppressants

Corticosteroid sparing agents, such as AZA 1-2 mg/kg/d, MMF 1000-1500 mg bd, or methotrexate (MTX) 10-20 mg weekly with folic acid, are commonly used, especially if higher doses of corticosteroids are required. These agents are believed to be effective, but need a prolonged period of time for their full impact to be seen.⁴⁷ Only AZA has been demonstrated to be effective by randomised trial but took 15 months to have any effect, and while MMF is widely used, the evidence base is poor, impacted by shorter, negative studies, it may also take greater than 12 months to be effective, which should be advised on initiation.⁴⁸ In patients in remission or with significant lymphopenia, the dose may be weaned, but relapse is common after complete cessation in patients who remain antibody positive.⁴⁹

PLEX and IVIg

PLEX and IVIg are useful in the treatment of acute, severe MG relapses, crises, pre-operatively, or rapidly worsening disease. Both treatments have the advantage of a rapid onset of action. Although PLEX and IVIg are reported to have equivalent efficacies in MG,⁵⁰ several groups have shown that patients with MuSK MG are more likely to respond to PLEX than to IVIg.^{18,51,52} Given that most immunosuppressant treatments have a delayed onset of action, PLEX and IVIg can be seen as adjunctive treatments until the benefits of immunosuppressants manifest.

PLEX aims to remove pathogenic antibodies from blood, by direct removal of immunoglobulin from serum. It leads to fast, but only short-term (3-4 weeks) improvement of myasthenia symptoms, and is therefore often used in the context of acute MG exacerbations, and sometimes on a regular basis for long-term management of disease.⁵³

IVIg consists of pooled immunoglobulins from donor blood and has been found to have short-term benefits in MG exacerbations comparable to PLEX.⁵⁴ Its efficacy has been studied when given as a bolus of 1–2 g/kg during severe exacerbations of MG and myasthenic crises,⁵⁰ as well as pre-operatively before thymectomy. However, doses of 1 g/kg have been shown to be equally effective as the higher dose.⁵⁵ It should be recognised that IVIg is a short-term symptomatic therapy that does not induce remission or change underlying disease activity.⁵⁶ Consequently, if a patient no longer has demonstrable features of MG, continuation of IVIg infusions is not warranted. Maintenance IVIg therapy should be reserved for when MG is uncontrolled or there are clear contraindications to escalating immunosuppressive therapies whilst awaiting the full effect of other immunotherapies. A defined treatment interval and anticipating trials of withdrawal should be discussed with patients prior to commencing treatment.

Optimising IVIg dosage

IVIg efficacy has been studied as a bolus of 1–2 g/kg given during severe exacerbations of MG and myasthenic crises⁹ and pre-operatively before thymectomy. Doses of 1 g/kg are equally effective as the higher dose under most circumstances.³⁷ Maintenance doses can range from 0.4 to 1 g/kg, but the amount per dose should be titrated to the patient's response, as long as no more than 1 g/kg every 4 weeks. That is, some patients can receive smaller doses more often than every 4 weeks.¹²

In a myasthenic crisis, some patients may experience relapse even after their significant initial improvement and may require short-term maintenance IVIg after their initial therapy. Reasons include that the effect from corticosteroid therapy may not be apparent until after 6 to 8 weeks or be insufficient, while the effect of IVIg therapy may wear off after 4 weeks.³⁸

Once the clinical features of MG have resolved, IVIg can generally be weaned. There is no established preventative role for continuing IVIg once MG is in pharmacologic remission.

Considering ideal body weight

Ig dosage has historically been based on a person's total body weight (TBW). However, this method may not be appropriate in patients who are clinically obese (BMI > 30 kg/m²), as Ig accumulates disproportionately in fluids compared to body fat.^{39,40} Where actual body weight exceeds ideal body weight (IBW), a common approach is to adjust Ig dosage for IBW, although this method needs further research.¹² Dose adjustments for IBW may be applied by the prescriber, at their discretion, or according to state/territory policy. Adjusted dosing for IBW is not recommended in patients aged less than 18 years, less than 152 cm in height, or who are pregnant. Where the dose-determining weight is greater than the patient's actual weight, use the actual weight to calculate the Ig dose.¹² It should also be noted that IBW dosing has not been trialled nor established for use in MG and has a very limited evidence base in clinical use. There is no evidence supporting the use of IBW dosing in MG of which we are aware. Ideal body weight dosing is not practiced by the authors of this paper but has been included at the request of the sponsor.

Cytotoxic agents

Cyclophosphamide and rituximab (RTX) are used as third-line remission induction agents in the treatment of refractory MG. Dosing should be the subject of specialist consultation.

Unlike other corticosteroid-sparing immunosuppressants, cyclophosphamide has a more rapid onset of action in MG, with clinical improvements typically seen within 3 months of treatment.^{57,58} These agents can be associated with significant side effects and long-term safety concerns but can be safely given with supervision. Cyclophosphamide is given in short pulses, which can be repeated monthly for 6 months. It has been associated with more rapid improvement from severe exacerbations and reduced corticosteroid requirements and, unlike most immunosuppressive drugs in MG, has been confirmed to work in a randomised controlled trial.⁵⁹ Administering an immunosuppressive such as MMF following the cyclophosphamide induction is suggested to minimise later relapse.⁵⁷

Efficacy of RTX has been suggested from a number of case series,⁶⁰ but was not confirmed in an unpublished but reported phase II study.⁶¹ MuSK MG appears to be particularly sensitive to RTX, resulting in this treatment option used early in this otherwise relatively difficult-to-treat variant.^{62,63} A recent article suggested RTX to be more beneficial in early AChR MG, as compared to a refractory cohort with established MG.⁶⁴ The long-term benefit of RTX in purely AChR antibody MG remains uncertain.⁶⁵

Emerging therapies

Subcutaneous Ig (SCIg) has recently become available in Australia for patients with chronic inflammatory demyelinating polyradiculoneuropathy as well as a number of immunological and haematological conditions, but is not currently available for MG. Transition from IVIg to SCIg is thought to be safe, should this option become available.⁶⁶

Depletion of pathogenic circulating immunoglobulins, using antagonists to the neonatal Fc receptor (FcRn inhibitors), has been explored in phase II studies and recently announced phase III studies. Efgartigimod and rozanolixizumab are two agents currently undergoing further trials.^{67,68} They induce rapid reduction of circulating IgG levels similar to PLEX.⁶⁹ Efgartigimod demonstrated impressive benefit in primary and secondary endpoints in a recent phase III randomised trial.⁷⁰

Eculizumab is a monoclonal antibody designed to bind to human terminal complement C5, thereby inhibiting mediation of proinflammatory cell chemotaxis by C5a and formation of the membrane attack complex by C5b.¹⁴ Eculizumab is used in complement mediated diseases, such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome. It has been shown to improve secondary outcomes but not the primary outcome in the REGAIN study.⁷¹

Neither the FcRn nor complement inhibitors are approved or funded for use in MG in Australia at the time of writing. However they may well assume a significant role in MG treatment in the future.

Based on previous experience with RTX, a number of B-cell depleting agents are currently being considered for treatment trials in MG. This includes monoclonal antibodies targeting CD20 (obinutuzumab), CD19 (inebilizumab) and B-cell activation factor – BAFF (belimumab), although phase II randomised controlled trials of belimumab and RTX have been negative.^{61,72,73}

Therapy-specific risks in the treatment of MG

Whilst MG is a highly treatable disease, it should be acknowledged that all treatments other than pyridostigmine do have risks of serious and sometimes irrevocable side effects. These are summarised in Table 4.

A consistent theme in MG treatment is balancing the dose-dependent side effects of corticosteroids with the immunosuppressive and drug-specific risks of the steroid-sparing drugs, and with the opportunity costs and lack of long-term benefit of IVIg and PLEX. Corticosteroids have clear high-frequency, well-known risks;⁴² research noted a small increase in the relative risk of death in an older population with giant cell arteritis, matched to local controls, following 12 months of corticosteroid use.⁷⁴ However, remission induction in MG without corticosteroids has not been shown to work in either studies or in practice, and corticosteroids are a mainstay of MG therapy.⁷⁵

Exercise with aerobic and resistance components is safe and feasible in MG, and while short-term fatigue can occur, it does not induce any long-term deterioration, but instead has numerous benefits.⁷⁶ We prescribe 6 hours of exercise per week as an offset to corticosteroid side effects.

The COVID-19 pandemic has raised particular concerns around immunosuppressive medications (reviewed separately).⁷⁷ In general, continuation of medications and control of the underlying disease should be prioritised. Initial reports of COVID-19 outcomes in patients with MG, including from the CAREMG study group, are not reassuring, with high complication and fatality rates.⁷⁸

Outcome monitoring

It is important to have standardised objective (physician reported) and subjective (patient reported) measures of outcome in MG on which to base therapeutic decisions. The qualifying Myasthenia Gravis Composite (MGC) criteria for access to IVIg in Australia are a combination of physician- and patient-reported outcomes for routine clinical use, which take 2–3 minutes only. The earliest Myasthenia Gravis Foundation of America (MGFA) scale relies on the distribution and severity of involvement but is insensitive to small changes. Newer tools from research trials appear more useful in monitoring fluctuations in disease severity and associated quality of life. These include the Quantitative Myasthenia Gravis Scale (QMGS) for clinical trials. The MG Impairment Index (MGII), MG Quality of Life (MG-QOL) score, and the MG activities of daily living (MG-ADL) questionnaire are patient-reported measures.^{79,80,81}

Monitoring summary

At each clinic visit the treating team should gauge:

- ▶ overall progress, change in MG, level of physical activity
- ▶ side effects, especially infections, malignancy
- ▶ physical exam – MGC components and any general examination aspects of concern
- ▶ perform standard assessment scales – MGC (doctor), MG-ADL, MGII.

Appropriate laboratory monitoring should be arranged depending on therapies used.

Table 4: Therapy-specific risks in the treatment of MG

Therapy	Onset of action	Time to maximal effect	Risks and side effects	Issues and monitoring	Comments
Rapid onset of action immunomodulators					
Pyridostigmine (Mestinon)/ Neostigmine	< 1 hr	3-4 hrs	Gastrointestinal Muscle twitching/ cramps Increased secretions	Myasthenic crisis	May worsen in MuSK MG or in excess dose
Corticosteroids	1-3 weeks	2-6 months (may be shorter for ocular)	Elevated blood sugar levels Hypertension Osteoporosis Impaired wound healing Gastritis Mood changes Increased/atypical infections Weight gain, fluid retention Cataracts	Use with caution – hypertension, diabetes, osteoporosis Monitor weight, BP, BSL, bone density	Higher dose onset may worsen acutely Exercise (aerobic and resistance) can offset side effects Consider bone loss prevention; only exercise, denosumab and bisphosphonates are effective
IVIg	2-3 days	1 week	Infusion reactions eg, headache, flu-like symptoms Rarely – thrombosis, renal failure, stroke, myocardial infarction ^{48,49}	No long-term benefit	Consider thrombosis prophylaxis in high risk with LMWH
PLEX	1-2 days	1 week	Hypotension Vascular access – infection ⁸²	No long-term benefit	Consider fistula or apheresis port ⁸³
Long-acting immunosuppressants and therapies					
Azathioprine	15+ months	2-3 years	Gastrointestinal Atypical infections ++Increased risk of skin malignancies General malignancy risk	Pre: TPMT Monitor FBC LFT Idiosyncratic reactions including late	Treatment-associated non-melanoma skin cancer is a major issue in Australia
Mycophenolate	>9 months	Not proven, 2-3 years	Gastrointestinal Atypical infections General malignancy risk	Teratogenic Monitor: FBC	Use is well established despite < 12-month duration negative trials

Therapy	Onset of action	Time to maximal effect	Risks and side effects	Issues and monitoring	Comments
Thymectomy	1 week – 2 years	3 years	Operative/ anaesthetic risks	Pre: Cardiac check	Prefer surgical unit with high currency
Methotrexate	Not proven	Not proven, 2–3 years	Gastrointestinal Liver toxicity Pneumonitis Pulmonary fibrosis Atypical infections	Teratogenic Monitor FBC EUC LFT	Use less well established; negative 12-month trial
Cyclophosphamide	3–4 months	6 months	Atypical infections Cytotoxicity Reduced fertility	Teratogenic Midcycle FBC EUC Dose adjustment	Neutropenic risk – dose adjustment PJP risk – prophylaxis Fertility – egg/ embryo/sperm bank
B-cell directed					
Rituximab	2–4 months	Not proven 2–6 months	Atypical infections Infusion reactions Impaired vaccine and novel infection responses	Pre-treatment: Vaccinate Pre: hepatitis B, core, hepatitis C Fetal immunodeficiency	Hepatitis B prophylaxis if latent infection. Longer-term infection rates, poor neoantigen immunity eg, COVID-19. Lasting and highly effective in MuSK, negative trial in AChR MG

BP = blood pressure; BSL = blood sugar level; COVID-19 = coronavirus disease 2019; EUC = electrolyte, urea, creatinine; FBC = full blood count; IVIg = intravenous immunoglobulin; LFT = liver function test; LMWH = low molecular weight heparin; MuSK = muscle-specific tyrosine kinase; PJP = Pneumocystis jiroveci pneumonia; PLEX = plasma exchange; TPMT = thiopurine methyltransferase test

Patient experience – setting treatment expectations and goals

A very important part of managing MG is understanding and explaining the typical disease and time course of the disease, both for the doctor and the patient. There are several short-acting therapies that can quickly improve MG but have no effect on the long-term course (pyridostigmine, IVIg, PLEX). However, drugs altering the immunological natural history that can put MG into remission work far more slowly than in other autoimmune diseases, with onset of any benefit being in months (corticosteroids, cyclophosphamide, RTX) to having no benefit until more than 1 year (AZA, MMF, MTX).

Understanding this timeline is critical as it underpins why combination or multiagent therapy enables short-term stabilisation with long-term remission as the objective, and what length of time a reasonable trial of therapy entails. It also helps to explain to the average patient that the first year after diagnosis can be challenging with fluctuating symptoms, many medical attendances including for infusion-based therapies, and new drugs. But over 2–3 years, pharmacologically assisted remission can be achieved in many and life can return to near normal.

However, due to the fluctuating symptoms associated with MG, managing patient expectations can be difficult, as objective assessments may not necessarily reflect patients' experienced symptom burden.⁸¹ A long-term optimism and explaining that the first year can be expected to be tough (but 'hang in there') can be very helpful to patients in coping with the diagnosis, as can linking a new patient in with patient associations. It also helps with trust, in the rather slow process, if this expectation is explained early.

Immunoglobulin treatment considerations

Treatment considerations in MG expose structural healthcare issues including different funding arrangements for the key 'rescue' therapies, IVIg and PLEX. Furthermore, none of the immunosuppressive treatments used routinely in the management of MG are actually indicated by the Therapeutic Goods Administration for this indication, with clinicians using these drugs entirely off label. There is no legal impediment to prescribing off label, however the onus is on the prescriber to defend their prescription for an indication that is not listed in the product information.¹⁹ It is recommended by the Council of Australian Therapeutic Advisory Groups that patients be explicitly advised of off-label prescriptions.²⁰

As a chronic health condition not infrequently diagnosed in young adults, MG can be associated with significant health costs over the lifetime of an individual. The greatest costs for publicly funded healthcare provision are associated with the use of 'rescue' therapies such as IVIg and PLEX, as well as the off-label use of expensive therapies such as RTX. There is limited comparative IVg versus PLEX cost data, but in the Canadian healthcare system, PLEX was less costly than IVIg for MG, based on combined clinical trial and health cost data.⁸⁴ The literature on cost of illness for patients with MG is extremely limited, but does highlight the relationship between added cost burden for patients with increasing severity of MG due to productivity losses and reliance on assistance with activities of daily living.⁸⁵

IVIg is a precious and limited resource. Each IVIg preparation is made from the pooled plasma of 3000–10,000 blood donors. Due to the high costs of manufacturing, the estimated cost of IVIg is \$1300–\$1700 per 70kg person at 0.4g/kg dose per day of treatment given. The cost of the product is shared between the Commonwealth and the relevant state or territory via the National Blood Authority (NBA). The demand for IVIg is shared across multiple medical specialities for the treatment of a wide variety of conditions, including immunodeficiencies and autoimmune diseases. Due to increasing demand, domestic supply is currently supplemented by imported IVIg.

In Australia, the NBA provides criteria on the contexts in which government funded IVIg may be prescribed given the potential scarcity and cost associated with use.¹⁷ Prescribers must seek authorisation through the [BloodSTAR](#) (Blood System for Tracking Authorisations and Reviews) portal by providing clinical information to establish that the request meets the NBA criteria. IVIg may be prescribed as a one-off for crisis or in preparation for surgery, or in the maintenance treatment of MG whereupon the criteria require a trial of weaning IVIg, or a reason provided why this is not able to be done, in recognition that IVIg should be regarded as a 'stop-gap' symptomatic treatment while introducing long-term immunotherapy.

PLEX is the other currently available 'rescue' therapy in the treatment for more severe MG. In Australia, the cost of PLEX is probably similar to that of IVIg, however the cost burden of PLEX is carried primarily by the hospital budget and may be relatively underfunded compared to IVIg. Two randomised controlled trials have compared PLEX and IVIg for MG.^{86,87} One study (without blinding) compared three exchanges versus 1.2 g or 2 g/kg IVIg and found no difference in a myasthenic muscular score.⁸⁷ In the second trial, blinded evaluators compared five exchanges with 2 g/kg IVIg and found no significant difference in QMG scores, although a trend favoured PLEX (Day 0–28 change in QMG: IVIg 2.6+/-4.0, PLEX 4.7+/- 5.7, p = 0.08).⁵⁴ Traditionally, PLEX has been seen as less desirable than IVIg due to the requirement for central venous access and the associated risk of infection. These barriers can be circumvented by the use of peripheral venous access, which is now available at many centres. PLEX may also be more effective than IVIg for some patients, in particular those with MuSK MG.^{10,18}

A cost comparison⁸⁸ into the use of IVIg for MG undertaken for the [Medical Services Advisory Committee \(MSAC\)](#) showed that where IVIg was costed at the estimated average annual maintenance dose used in Australia (492 g/patient), it was more expensive than a low-intensity PLEX regimen, but less expensive than intensive weekly PLEX. Low-dose IVIg also appeared less expensive than low-intensity PLEX, and high-dose IVIg monthly appeared less expensive than high-intensity PLEX (Table 5).

Although findings were uncertain due to various modelling limitations (such as uncertain equivalence of benefit, no adverse events included, no treatment discontinuations or trials off therapy, no dosage tapering), they demonstrate the considerable added expense of IVIg doses in the higher ranges. What is more apparent is the very high real cost of IVIg or PLEX when required continuously for years, which rapidly becomes disproportionate to the costs of generic immunosuppressive medications and/or thymectomy.

Table 5: Annualised cost comparison for IVIg versus PLEX for MG maintenance therapy

Therapy		Total discounted cost (1 year)
IVIg	NBA data-derived annual dose	\$34,516
PLEX	Low intensity (every 4 weeks)	\$33,362

The use of expensive and/or off-label therapies remains a constant issue for the treatment of rare diseases such as MG. Rarer diseases are often a low priority for pharmaceutical-sponsored clinical trials given the likelihood of lower commercial returns compared with studies in more common diseases, as well as the difficulties in recruitment. Instead, clinicians often rely on case series and small, often underpowered, trials to help guide treatment decisions. Patient registries such as [MGBase](#), are likely to prove to be powerful and cost-effective tools for expanding our understanding of diseases and their treatments, ultimately improving the overall quality of care for patients.

Appendix A

Table 6: Standard therapies in MG⁴⁷

Therapy	Onset of action	Time to maximal effect	Risks and side effects	Issues and monitoring	Comments
Rapid onset of action immunomodulators					
Pyridostigmine (Mestinon)/ Neostigmine	< 1 hr	3–4 hrs	Gastrointestinal effects including cramping and diarrhoea Muscle twitching/ cramps Increased salivation and lacrimation	Discontinue in myasthenic crisis	Initial therapy Temporary symptom improvement without affecting prognosis Less effective in MuSK MG or could produce side effects

A typical dosing regimen starts at 30 mg orally, three times daily, then depending on response and tolerability, the daily dose can be increased every 4 to 7 days to a maximum of 120 mg daily given as two to six smaller doses. Use the lowest effective dose and review after 4 to 6 weeks. If the response is inadequate, consider immunosuppression. Doses should be given when the patient is most fatigued (eg, 30 to 45 minutes before meals when the patient has bulbar weakness). Dose escalation is often limited by side effects, including gastrointestinal cramping, diarrhoea and muscle cramps. Propantheline or mebeverine could decrease cholinergic effects. If the patient is asymptomatic following the introduction of prednisolone only, withdraw pyridostigmine slowly over a few weeks. Stopping pyridostigmine avoids wrongly interpreting its adverse effects (muscle twitching or cramping) as disease activity.

Corticosteroids	1–3 weeks	2–6 months (may be shorter for ocular)	Elevated blood glucose levels Hypertension Osteoporosis Impaired wound healing Gastritis Mood changes Increased/atypical infections Weight gain, fluid retention Cataracts HPA axis suppression	Use with caution – hypertension, diabetes, osteoporosis Monitor weight, BP, BGL, bone density	Fast acting Side effects especially in supraphysiological doses (> 8 mg/day) Escalation and de-escalation of dose required Exercise (aerobic and resistance) may offset side effects Consider bone loss prevention; exercise, denosumab and bisphosphonates are effective
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A typical initiation protocol for generalised MG is 5–10 mg orally, daily in the morning, increasing by 5–10 mg every week to 0.5–1 mg/kg (up to 75 mg) daily. After 4 to 6 weeks, reduce daily dose by 5 mg every 2 weeks to 25 mg daily, then lower doses according to response and side effects. Introduce a corticosteroid-sparing drug soon after initiation if long-term corticosteroid therapy is likely.

Therapy	Onset of action	Time to maximal effect	Risks and side effects	Issues and monitoring	Comments
IVIg	2-3 days	1 week	Infusion reactions eg, headache, flu-like symptoms Rarely – thrombosis, renal failure, stroke, myocardial infarction ^{48,49}	No long-term benefit	In high-risk patients consider thrombosis prophylaxis with LMWH
PLEX	1-2 days	1 week	Hypotension Vascular access – infection ⁵⁰	No long-term benefit	Consider access if long-term therapy is required

Long-acting immunosuppressants and therapies

Azathioprine (AZA)	15+ months	2-3 years	Gastrointestinal effects (nausea, vomiting, cramping) Atypical infections Increased risk of skin malignancies General malignancy risk	Pre: TPMT Monitor FBC LFT Idiosyncratic reactions	Treatment-associated non-melanoma skin cancer is a major issue in Australia
Mycophenolate (MMF)	> 9 months	Not proven, 2-3 years	Gastrointestinal effects (nausea, vomiting, abdominal pain, diarrhoea) Atypical infections General malignancy risk	Teratogenic Monitor: FBC	Use is well established despite < 12-month duration negative trials
Methotrexate (MTX)	Variable	Not proven, 2-3 years	Gastrointestinal effects (nausea and vomiting) Liver toxicity Pneumonitis Pulmonary fibrosis Atypical infections	Teratogenic Monitor FBC EUC LFT	Use less well established; negative 12-month trial

Commonly used medicines and doses include AZA 1-2 mg/kg/d, MMF 500-1500 mg twice daily, or MTX 10-20 mg weekly with folic acid, especially if higher doses of corticosteroids are required. These agents are effective, but their full effect requires prolonged periods of therapy.²¹ A randomised trial showed AZA's efficacy in a median of 15 months, but the evidence for MMF is poor, impacted by shorter, negative studies.⁵¹ For patients in remission or with significant lymphopenia, the dose may be weaned, but relapse is common after complete cessation in patients who remain antibody positive.⁵²

Therapy	Onset of action	Time to maximal effect	Risks and side effects	Issues and monitoring	Comments
Cyclophosphamide	3-4 months	6 months	Atypical infections Cytotoxicity Reduced fertility	Teratogenic Midcycle FBC EUC Dose adjustment	Neutropenic risk - dose adjustment PJP prophylaxis Fertility - egg/embryo/sperm bank

Cyclophosphamide has a rapid onset of action and could achieve clinical improvements within 3 months of treatment.^{53,54} It is associated with more rapid improvement among people with severe exacerbations, and with reduced corticosteroid requirements. Unlike most immunosuppressive drugs for MG, it has been confirmed to work in a small randomised controlled trial. Further, adding an immunosuppressive such as MMF following cyclophosphamide induction could minimise later relapse.⁵³ Typically, cyclophosphamide is given intravenously monthly for 6 months and may be associated with significant side effects.⁵⁵

B-cell directed therapies

Rituximab (RTX)	2-4 months	Not proven 2-6 months	Atypical infections Infusion reactions Impaired vaccine and novel infection responses	Pre: Complete vaccinations Screen: Hepatitis B, core, hepatitis C Fetal immunodeficiency	Hepatitis B prophylaxis if latent infection Longer- term infection rates, poor neoantigen immunity eg, COVID-19 Lasting and highly effective in MuSK, negative trial in AChR MG
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Efficacy of RTX has been suggested from several case series,⁵⁶ but was not confirmed in an unpublished but reported phase II study,⁵⁷ nor in other AChR MG series. MuSK MG appears to be particularly sensitive to RTX, resulting in this treatment option being used early in this otherwise relatively difficult-to-treat variant.^{58,59} A recent article suggested RTX could be more beneficial for patients with early AChR MG, as compared to a refractory cohort with established MG.⁶⁰

Cyclosporin, tacrolimus

Cyclosporin, at doses of 3.5 mg/kg/day, is a potent immunosuppressant which is not teratogenic.^{38,61} Efficacy could be achieved in 3 months, but patients may experience significant side effects such as hypertension, altered glomerular filtration rates, nephrotoxicity, tremor, and females could experience hirsutism. Tacrolimus has a similar efficacy and side-effect profile. Both agents could have a role in younger patients with disease refractory to other steroid-sparing immunosuppressants.³⁸

AChR = acetylcholine receptor; AZA = azathioprine; BP = blood pressure; BGL = blood glucose level; EUC = electrolytes, urea, creatinine; FBC = full blood count; HPA axis = hypothalamic-pituitary-adrenal axis; IVIg = intravenous immunoglobulin; LFT = liver function test; LMWH = low molecular-weight heparin; MG = myasthenia gravis; MMF = mycophenolate; MTX = methotrexate; MuSK = muscle-specific tyrosine kinase; PJP = *Pneumocystis jirovecii* pneumonia; TPMT = thiopurine methyltransferase.

Appendix B

Access to Ig

In Australia, Ig products, like other blood products, are supplied at no direct cost to eligible patients under the [National Blood Agreement](#) (the Agreement),¹⁷ and are managed by the National Blood Authority (NBA). The Agreement's primary objectives are:

- ▶ to provide an adequate, safe, secure, and affordable supply of blood products, blood-related products and blood-related services in Australia; and
- ▶ to promote safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

Under the Agreement and related national blood arrangements, the NBA manages contracts with domestic and international suppliers of Ig to ensure demand for supply is met and manages a contract with the Australian Red Cross Lifeblood (Lifeblood) to collect blood and blood plasma from voluntary donors to support production and manufacture of Ig products for supply in Australia.

As collecting, manufacturing, and distributing Ig products is particularly expensive, and there is a limited supply, the NBA has a dedicated Ig Governance Program to manage Ig access, ensuring it is available for those who need it most. All healthcare professionals directly involved in the prescription, use and management of Ig have defined roles and obligations to ensure that Ig products are properly used and managed in line with the nationally agreed rules and obligations. Details are set out in [The National Policy: Access to Government-Funded Immunoglobulin Products in Australia](#).

Rules governing patient eligibility for Ig funded under national blood arrangements are set out in the [Criteria for the clinical use of immunoglobulin in Australia](#) (Criteria). The Criteria are evidence-based and are developed and maintained by a national panel of health experts, in collaboration with federal, state and territory governments. They clearly articulate the medical conditions and circumstances for which the use of Ig funded under national blood arrangements is permitted, based on clinical appropriateness and the availability of safe, effective, and cost-effective alternative treatments.

To access Ig under the Agreement, medical officers are required to submit an authorisation request through the national online system [BloodSTAR](#), accessed through the NBA's online BloodPortal. The system is used to manage the authorisation request and review process and ensures that access to Ig products is consistent with the National Policy. Lifeblood is contracted by the NBA to review and authorise applications and provide advice on eligibility as required.

Patients that are ineligible to access Ig products under the Criteria may be able to access Ig through a [Jurisdictional Direct Order](#) at a cost to the approved health provider, or directly from suppliers at a personal cost.

Further information is available on the NBA's website at, <https://www.blood.gov.au/Ig> with online training courses available through BloodSafe eLearning at: <https://learn.bloodsafelearning.org.au/categories#immunoglobulin-courses>.

Approved indications

Two blood product based therapies are available for MG: IVIg and PLEX. Both treatments have the advantage of a rapid onset of action and are non-inferior to each other.⁹ Some studies suggest that people with MuSK-MG may be more likely to respond to PE than IVIg).^{13,14,15} PLEX removes pathogenic antibodies from the blood through the removal of serum Ig.¹⁶ It can result in fast but short-term (3 to 4 weeks) improvement in MG symptoms. IVIg is an antibody immune modulator therapy manufactured from pooled donor blood Ig – a finite and scarce resource. It is indicated as an adjunctive treatment until the benefits of immunosuppressant treatments are apparent.

The NBA has three approved indications for IVIg in MG:¹²

- ▶ Myasthenic crisis as an alternative treatment to PLEX.
- ▶ MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms, or respiratory involvement, as an alternative treatment to PLEX.
- ▶ As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

The [Criteria](#) should be referred to for a current list of qualifying conditions and circumstances where the use of Ig products is considered to be clinically appropriate.

Evidence base for indications

To ensure that Ig therapy is directed to those who need it most, the MSAC contracted a systematic search and review of published and unpublished literature on the use of Ig for MG. The literature search was conducted in March 2019, using major medical literature databases to identify relevant studies and systematic reviews published since January 1980. A total of 5918 articles were identified and screened: 198 were utilised for full-text review, and a final number of 29 individual articles were included in the review.¹⁸

Indication one: treatment of acute myasthenic crisis

Guidelines from the American Academy of Neurology, European Federation of Neurological Societies, and the IVIg Hematology and Neurology Expert Panel recommend IVIg as adjunctive therapy in the treatment of acute exacerbation of MG. These guidelines state that there is insufficient evidence to recommend IVIg as maintenance therapy for chronic MG.²⁵ The recommendations correspond with the NBA's criteria that IVIg is only for life-threatening myasthenic crisis, respiratory insufficiency requiring intubation, assisted ventilation, and is inappropriate for managing ocular MG symptoms.¹⁸

Compared to PLEX, the evidence base shows that IVIg has superior safety and non-inferior effectiveness when used in the treatment of MG.¹⁸ For example, change in myasthenia muscle score (MMS)*, at 15 days from baseline was similar between IVIg versus PLEX. For myasthenia severity scale (MSS), the change at 14 days from baseline was only statistically significant in the PLEX group, although there was improvement in both groups (Table 7).^{21,22,23}

* MMS = myasthenia muscle score is the sum of nine independent observations, four items assessing the muscular strength of the trunk and limbs and five items assessing the cranial muscles. MSS = myasthenia severity scale: dyspnoea: 1 (intubated) to 4 (none); cough: 1 (intubated) to 3 (normal); ocular: 1 (weakness at rest) to 3 (none); bulbar 1 (weakness at rest) to 3 (none); extremities: 1 = worst affected muscle 3/5 or less, 2 = worst-affected muscle 4/5 motor strength or weakness on fatigue, 3 = no detectable weakness.

Similarly, a Cochrane review showed comparable trends, despite problems with inference or prediction due to poor trial designs. The review included four poorly designed and underpowered randomised controlled trials (containing a total of 147 children and adult patients) that found benefit but no significant difference between IVIg and PLEX, and no significant difference between IVIg and methylprednisolone. One of the four studies found no benefit for IVIg therapy, that is, no significant difference between IVIg and placebo.²⁴

Table 7: The evidence for IVIg versus PLEX^{21,22,23}

Patient or population: Patients with moderate to severe MG in or at risk of myasthenic crisis

Intervention: IVIg; IVIg 1 g/kg

Comparison: PLEX; IVIg, 2 g/kg

Quality assessment			Effect			
Outcome Comparison	Participants Studies	Quality of evidence*	Intervention result	Comparator result	Difference	Interpretation
Change in MMS (change in score at 15 days from baseline) IVIg vs PE	n = 87 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	15.6 ± 16.0	16.6 ± 16.0	Mean difference -1 (95% CI -7.72, 5.72), p = 0.77	There was no difference in the change in MMS occurring between groups
Change in MSS (change in score at 14 days from baseline) IVIg vs PE	n = 54 retrospective cohort	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0 confounding is likely to give spurious effect	2.8 ± 0.71	4.2 ± 0.57		Improvement in symptoms from baseline was only statistically significant in the PLEX group although there was improvement in both groups
Time to treatment response (median days to response) IVIg vs PE	n = 87 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	15.0	9.0	RR = 0.67 (95% CI 0.38, 1.18), p = 0.14	Time to treatment favoured PLEX but the difference was not statistically significant
Change in MMS (change in score at 15 days from baseline) IVIg 1 g/kg vs IVIg 2 g/kg	n = 168 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	19.33 ± 16.48	15.49 ± 15.4	Mean difference 3.84 (95% CI -0.98, 8.66), p = 0.12	There was no difference in the change in MMS occurring between groups

CI = confidence interval; IVIg = intravenous immunoglobulin; MMS = myasthenia muscle score; MSS = myasthenia severity scale; PLEX = plasma exchange; RCT = randomised controlled trial; RR = relative risk. *Key: 0 = not serious, -1 = serious, -2 = very serious.

Indication two: preoperative use in MG

A study by Jensen and Brill showed that, although symptoms improved in IVIg or PLEX groups following surgery, there was no difference in symptom change (Osserman grade) between patients treated with IVIg or PLEX (Table 8).^{18,26} Kernstine (2005) utilised PLEX or IVIg for pre-operative preparation in patients with advanced disease, bulbar symptoms, or poor pulmonary function.²⁷ However, the corollary is that without these features, the treatment is unnecessary.¹²

Table 8: The evidence for IVIg versus PLEX in pre-operative treatment²⁶

Patient or population: Patients with moderate to severe MG preparing for surgery

Intervention: IVIg

Comparison: PLEX

Quality assessment			Effect			
Outcome Comparison	Participants Studies	Quality of evidence*	Intervention result	Comparator result	Difference	Interpretation
Change in Osserman grade (mean change in grade from baseline) IVIg vs PLEX	n = 18 retrospective cohort	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Other: 0	0.78 ± 0.83	1.00 ± 0.71	p = 0.55	There was no difference detected between groups
Change in QoL (% patients with perceived benefit from treatment) IVIg vs PLEX	n = 18 retrospective cohort	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1 Other: 0	56%	100%	-46% (95% CI 4.75%, 73.0%), p = 0.029	More patients perceived a benefit following PLEX treatment Small patient numbers make this result unreliable

CI = confidence interval; IVIg = intravenous immunoglobulin; PE = plasma exchange; QoL = quality of life.

*Key: 0 = not serious, -1 = serious, -2 = very serious.

Indication three: maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects

The evidence demonstrated an incremental benefit in symptom improvement using QMGs for adult patients treated with IVIg on top of standard maintenance therapies, but the effect peaked at 14 days then decreased. Three studies showed a trend for greater improvement in patients given PLEX compared with IVIg (as measured by QMGs) at 28 days and 16 weeks from the start of treatment, with the strongest improvement in symptoms seen in the first 2 weeks.¹⁸ Likewise, Hellman et al. showed that IVIg could improve MG with ongoing use, but it does not induce remission or alter the natural history of the disease.^{12,28} Similarly, the Asia-Pacific Advisory Group recommends using IVIg over a single day to treat MG exacerbations in myasthenic crisis or patients with severe weakness poorly controlled with other agents.²⁹ However, the group does not support IVIg for maintenance in stable moderate or severe MG except when alternatives have failed, and IVIg has shown benefit.^{12,29} These findings suggest IVIg should be a transitional therapy while using short-term medicines such as pyridostigmine and introducing effective immunotherapy.^{12,28}

Projected demand for Ig therapy

Multiple medical specialties use IVIg for treating a wide variety of conditions, including immunodeficiencies and autoimmune diseases. Due to increasing demand, imported IVIg products supplement domestic supply. Demand across the three MG indications projected to the year 2024 (Table 9), demonstrates increasing costs and pressure on supply. IVIg is a precious and limited resource; each preparation is made from the pooled plasma of 3000–10,000 blood donors. Due to high manufacturing costs, a standard weight dose per day (0.4 g/kg) cost \$1300 to \$1700. The Commonwealth and the relevant state or territory, via the NBA, share the cost of the products.¹⁸

Table 9: Demand for IVIg in costs and quantity to year 2024¹⁸

	2019–20	2020–21	2021–22	2022–23	2023–24
Cost per gram of Ig	\$60.41	-	-	-	-
Patients under indication one	223	241	258	276	294
Grams issued for indication one	53,903	58,193	62,482	66,772	71,061
Cost for indication one	\$3,256,280	\$3,515,439	\$3,774,538	\$4,033,697	\$4,292,795
Patients under indication two	37	39	42	45	48
Grams issued for indication two	5989	6466	6942	7419	7896
Cost for indication two	\$361,795	\$390,611	\$419,366	\$448,182	\$476,997
Patients under indication three	1046	1128	1211	1293	1376
Grams issued for indication three	539,034	581,928	624,822	667,716	710,610
Cost for indication three	\$32,563,044	\$35,154,270	\$37,745,497	\$40,336,724	\$42,927,950
Total number of patients (across all indications)	1306	1408	1511	1614	1718
Total number of grams issued (across all indications)	598,926	646,587	694,246	741,907	789,567
Total cost of Ig (across all indications)	\$36,181,120	\$39,060,321	\$41,939,401	\$44,818,602	\$47,697,742
Total cost of Ig for the Commonwealth	\$22,794,105	\$24,608,002	\$26,421,823	\$28,235,719	\$30,049,578
Cost for the states	\$13,387,014	\$14,452,319	\$15,517,578	\$16,582,883	\$17,648,165

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