Myasthenia gravis (MG)

Condition for which Ig has an established therapeutic role.

Specific Conditions	• Myasthenia gravis (MG)
Indication for Ig Use	• Myasthenic crisis as an alternative treatment to plasma exchange • MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange • As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects
Level of Evidence	Clear evidence of benefit (Category 1)
Description and Diagnostic Criteria	Myasthenia gravis (MG) is an autoimmune disease associated with the presence of antibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Some patients with myasthenia gravis are antibody negative. Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, namely levator palpebrae, extraocular, bulbar, limb and respiratory muscles. Patients usually present with unilateral or bilateral drooping of eyelid (ptosis), double vision (diplopia), difficulty in swallowing (dysphagia) and proximal muscle weakness. Weakness of respiratory muscles can result in respiratory failure in severe cases or in acute severe exacerbations (myasthenic crisis). Diagnosis is suspected based on the clinical picture described above, without loss of reflexes or impairment of sensation. Repetitive nerve stimulation typically shows a decreasing response at 2–3 Hz, which repairs after brief exercise (exercise facilitation). Edrophonium can be used for confirmation. Other useful investigations include serum anti-AChR or MuSK antibody titre, or single-fibre electromyography (SFEMG).
Justification for Evidence Category	The Cochrane review of seven randomised controlled trials (RCTs) (Gajdos et al 2012) found: • benefit but no significant difference between intravenous immunoglobulin (IVIg) and plasma exchange, for worsening myasthenia gravis (MG) • no significant difference between IVIg and methylprednisolone (this was a very limited study of questionable value). Gajdos (2005) compared in a 173-person RCT 1 g/kg versus 2 g/kg and found significant improvement in the myasthenic muscular scores (15.49 for 1 g/kg versus 19.33 for 2 g/kg; difference not significant but noting a trend). This suggests that the routine dose for worsening MG should be 1 g/kg unless circumstances warrant the higher dose (such as a patient in crisis or at risk of crisis). In this study, IVIg was given in a single day, although in Australia we have tended to space it out. An additional observation not specified as a primary endpoint was that IVIg was generally ineffective for diplopia. There is insufficient placebo-controlled evidence for the use of IVIg as a steroid-sparing agent or before thymectomy in stable MG, although multiple case reports suggest benefit in this context. Kernstine (2005) suggested that preoperative preparation with plasma exchange (PLEX) or IVIg should be considered for patients with advanced disease, bulbar symptoms, or poor pulmonary function. The corollary is that treatment is generally not required for patients without those features. Effectiveness of IVIg is equivalent to PLEX, but IVIg may be easier to administer than PLEX, which is also not available in some centres. The differing risks of these treatments should also be taken into account, including IV line insertion risks, line sepsis and haemodynamic effects for PLEX, and inflammatory and thrombotic consequences of IVIg. Several other important series have been published noting these were non-randomised and retrospective: Guptill (2011) published that PLEX is more effective than IVIg in MuSK antibody associated MG and this accords with other groups. Hellman (2014) published that IVIg, while improving MG with chronic use, does not induce remission or alter the natural history of the disease. Therefore, the Specialist Working Group suggests IVIg should be regarded as a stopgap while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy. The Quantitative MG Score (QMGS) (Bedlack 2005) has been the rating scale most commonly used in MG trials, and a score of greater than 11 has been shown to be a predictor of response to IVIg or PLEX (Katzberg 2012). However, the QMGS is a labour-intensive scale for trial use, and for clinical use the abbreviated MG Composite score (MGCS) has been recommended. This composite includes only items routinely examined and key patient reported symptoms (Burns 2010). An improvement of greater than or equal to three on the MGCS has been shown to have clinical significance. A lowest score predictive of response to IVIG has not been established for the MGCS to date.

Diagnosis Requirements	A diagnosis must be made by a Neurologist.
Qualifying Criteria for Ig Therapy	Myasthenic crisis as an alternative treatment to plasma exchange • Myasthenic crisis with respiratory insufficiency requiring intubation and assisted ventilation OR • Patient at risk of myasthenic crisis displaying symptoms of respiratory insufficiency such as persistent difficulty with speech, difficulty chewing or swallowing and/or shortness of breath on minimal activity AND • Clinical assessment confirms severe disability as measured by the Myasthenia Gravis Composite (MGC) score of at least four points. MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange • Surgery is planned AND • The patient has advanced MG disease, bulbar symptoms and/or respiratory involvement As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects • The patient has moderate to severe Myasthenia Gravis consistent with a Myasthenia Gravis Composite (MGC) score of at least four points AND • At least two other treatments are ineffective, are contra-indicated, unavailable or caused intolerable side effects **IVIg should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy**. IVIg should be used for four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned. Review by a neurologist is required within four months and annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.
Exclusion Criteria	Pure Ocular Myasthenia Gravis
Review Criteria for Assessing the Effectiveness of Ig Use	Myasthenic crisis as an alternative treatment to plasma exchange **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Improvement in symptoms of myasthenic crisis

MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange

Review is not mandated for this indication however clinical effectiveness of Ig therapy may be assessed by:

- Improvement in respiratory/bulbar symptoms and/or successful preparation for surgery

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

IVIg should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy.

IVIg should be used for four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Improvement in fatigability and weakness as measured by a Myasthenia Gravis Composite (MGC) score of at least three points less than the qualifying score

  OR

- The patient with severe disease continues to report improvement in symptoms and disability post infusion, with end-of-cycle deterioration

AND

- At least two other treatments are being prescribed concurrently

  OR

- Unable to be prescribed two other treatments concurrently, including:
  - Anticholinesterase inhibitor
  - Corticosteroids
  - Azathioprine
  - Methotrexate
  - Cyclophosphamide
  - Cyclosporin
  - Mycophenolate mofetil
  - Monoclonal antibodies
  - Plasma exchange
  - Thymectomy

On review of a continuing authorisation period

- Stability in fatigability and weakness as measured by a Myasthenia Gravis Composite (MGC) score compared to the previous review and less than the qualifying score

  OR

- The patient with severe disease continues to report improvement in symptoms and disability post infusion, with end-of-cycle deterioration

AND

- At least two other treatments being prescribed concurrently

  OR

- Unable to be prescribed two other treatments concurrently, including:
  - Anticholinesterase inhibitor
  - Corticosteroids
  - Azathioprine
  - Methotrexate
  - Cyclophosphamide
  - Cyclosporin
  - Mycophenolate mofetil
  - Monoclonal antibodies
  - Plasma exchange
  - Thymectomy

AND

- A trial of weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a reason provided as to why a trial is not planned

Dose

Myasthenic crisis as an alternative treatment to plasma exchange

- **Dose during myasthenic crisis (IVIg)** - 1–2 g/kg in 2 to 5 divided doses

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange

- **Pre-surgery dose (IVIg)** - 1–2 g/kg in 2 to 5 divided doses

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

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

- **Induction Dose (IVIg)** - 1–2 g/kg in 2 to 5 divided doses

  Note: A dose of 1 g/kg has been demonstrated to be equally effective as 2 g/kg for induction prior to maintenance therapy. A dose of 2 g/kg should be reserved for patients with particularly severe disease.
- **Maintenance Dose (IVIg)** - 0.4–1 g/kg, 4–6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 1 g/kg may be given in any four week period. This might be by smaller doses more frequently than monthly.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

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