### Specialist Working Group for Neurology

#### Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

| **ITEM** | **CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA EDITION 2** | **PROPOSED REVISIONS TO THE CRITERIA**  | **RATIONALE FOR PROPOSED CHANGE****(A) Administrative)****(B) Progressive** **(C) Programmed** |
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| Condition Name | **Myasthenia gravis (MG)** | **Myasthenia gravis (MG)** |  |
| Specialty | Neurology | Neurology |  |
| Chapter | 5 | 5 |  |
| Specific Conditions |  |  |  |
| Level of Evidence | Clear evidence of benefit ([Category 1](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-1)). | Clear evidence of benefit ([Category 1](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-1)). |  |
| Justification for Evidence Category | A Cochrane review of four RCTs (a total of 147 children and adult patients) found benefit but no significant difference between IVIg and plasma exchange, and no significant difference between IVIg and methylprednisolone. One of the four studies found no benefit of IVIg (i.e. no significant difference between IVIg and placebo). The individual trials were of poor design and some had small numbers of participants, so more research is needed (Biotext 2004).Anecdotal evidence of efficacy has come from clinicians. There is insufficient placebo-controlled evidence for IVIg use as a steroid-sparing agent or before thymectomy in stable MG, although multiple case reports suggest benefit in this context.The Asia–Pacific Advisory Group (2004) supports the use of IVIg over a single day for the treatment of myasthenia gravis exacerbations, in myasthenic crisis, or in patients with severe weakness poorly controlled with other agents. It does not support the use of IVIg for maintenance in stable moderate or severe MG unless other therapies have failed and IVIg has shown benefit.Effectiveness of IVIg is equivalent to steroids and plasma exchange but IVIg may be easier to administer than plasma exchange and avoids the side effects of steroids. | 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 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. Kernstein (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 Sore (QMGS) (Bedlack 2005) has been the rating scale most commonly used in MG trials and a score of >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 ≥3 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. | This section has been significantly revised and updated. This section has been revised and has informed definition of the eligibility criteria. Specialist Working Group recommends Ig should be regarded as a stopgap while using short term drugs such as pyridostigmine and while introducing effective immunotherapy. |
| Description and Diagnostic CriteriaThere should be no change the published text | 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 SFEMG (single-fibre electromyography). | 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). |  |
| Diagnosis is required |  Mandatory diagnosis and assessment by a neurologist; | By which speciality | Yes - Neurologist | Unchanged  |
| Diagnosis must be verified |  No | By which speciality | No |  |
| Exclusion Criteria |  |  |  |
| Indications | As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects. | 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. | Indications are retained however, The first indication has been revised into two to support clearer eligibility criteria including severity assessment and to differentiate use during myasthenic crisis from pre-surgery where use is now limited to patients with advanced disease, bulbar symptoms or respiratory involvement. (A) |
| Qualifying Criteria | Mandatory diagnosis and assessment by a neurologist;ANDAs an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy;ORAs maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects. | **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 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 or bulbar symptoms 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 MG as assessed by a Myasthenia Gravis Composite Score of at least four points

AND* At least two other alternative treatments have been ineffective, contra-indicated 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*.* | SWG discussion confirmed that follow up with clinical authors of scoring systems has identified that a lower threshold of responsiveness does not correlate to Myasthenia Gravis Composite (MGC) Score - but MGC will show a minimally significant difference. Selection of a level for moderate or severe is hard as ‘moderate’ is not defined. SWG proposal is to demonstrate benefit using a modest score of 4 out of 50 to qualify - given that it is possible to have moderate weakness (50% of normal) isolated to the hip girdle (rating 4). Lowest possible technical score by MGC is 4 still gives the patient the opportunity to improve by 3 at review. The single disability evaluation measure provides comparable data across all patients nationally. MGC Score has been validated in research trials, no equipment required and can be performed in 2 minutes. Reference to the scoring method will be available in the system. Reference: MGC (Neurology 2010;74:1434-1440)The SWG confirmed that the purpose of the criteria for maintenance therapy is to get prescribers to think about the level of weakness, and require that they have tried alternative therapies. Discussion noted that a number of the alternative medications were high cost drugs and may not be accessible for all patients, however, some views regarded that alternative therapies other than just steroids and one other should have been tried. It was agreed that there would be the occasional patient and circumstances where only 2 may be possible and IVIg should be given earlier. It was agreed that until an effective peer “appeals” or review process is established to support appropriate use in such circumstances, it was inappropriate to make the criteria any tighter. The SWG noted that until that time, the qualifying value should be 2 medications. It was acknowledged that use is likely remaining higher as a result. Types of alternative treatments include: * Anticholinesterase inhibitor
* 3,4-Diaminopyridine
* Corticosteroids
* Plasma exchange
* Thymectomy
* Azathioprine
* Methotrexate
* Cyclophosphamide
* Cyclosporin
* Mycoplenolate mofetil
* Monoclonal antibodies
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| Review Criteria | IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned.ReviewRegular review by neurologist is required: frequency as determined by clinical status of patient. Initial review three to six monthly.For stable patients on maintenance treatment, review by a neurologist is required at least annually.EffectivenessClinical documentation of effectiveness is necessary for continuation of IVIg therapy.Effectiveness can be demonstrated by improvement in fatigability and weakness.Various scores can be used, including:forward arm abduction time (up to a full five minutes); Quantitative Myasthenia gravis score (Duke); respiratory function (e.g. forced vital capacity); quantitative dynamometry of proximal limb muscles; variation of a myasthenic muscular score (MSS). | **Myasthenic crisis as an alternative treatment to plasma exchange.**Review is not mandated for this indication. **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.**As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.**IVIg should be used for four months (induction + 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 at the latest and annually thereafter. Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.Effectiveness can be demonstrated by improvement in fatigability and weakness**On review of an initial authorisation period** * Improvement in fatigability and weakness as measured by a Myasthenia Gravis Composite Score of at least three points less than the qualifying score.

**On review of a continuing authorisation period*** Stability in fatigability and weakness as measured by a Myasthenia Gravis Composite Score that is similar to the previous review and less than the qualifying score.
 | Myasthenic Crisis is one-off therapy - no review is required. However, if a second dose was required, the period between doses should be at least 2-4 weeks.One-off therapy, no review is required.All patients that are responders will have demonstrated a benefit after induction plus 3 maintenance cycles rather than waiting for 6 months / courses. Consistency has been maintained with CIDP and other conditions.  |
| Dose | **Maintenance**: 0.4–1 g/kg, 4–6 weekly.**Induction or before surgery, or during myasthenic crisis**: 1–2 g/kg in 2 to 5 divided doses. Aim for minimum dose to maintain optimal functional status.Note: smaller dosage may be of greater efficacy.Refer to the current product information sheet for further information.The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. | **Myasthenic crisis as an alternative treatment to plasma exchange.****Induction or during myasthenic crisis:** 1–2 g/kg in 2 to 5 divided doses. If a second one-off dose is required, it must not be given before 2-4 weeks. 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.****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:** 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.****As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.****Induction** 1-2 g/kg in 2 to 5 divided dosesNote: 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:** 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 divided 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.** | The comment regarding smaller doses being more efficacious is incorrect and has been deleted. While lower doses are not more efficacious, the patient should be titrated to the lowest dose possible.A study has failed to show any significant difference between 1 and 2 g for induction therapy prior to maintenance. Script added to this effect. |

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