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, SECOND EDITION (CRITERIA)	PROPOSED CHANGES TO THE CRITERIA	RATIONALE FOR PROPOSED CHANGES
Condition Name	**Multifocal motor neuropathy (MMN)**	**Multifocal motor neuropathy (MMN)**	
Specialty	Neurology	Neurology	
Chapter	5	5	
Specific Conditions			
Level of Evidence	Clear evidence of benefit (Category 1).	Clear evidence of benefit (Category 1).	
Justification for Evidence Category	The Biotext (2004) review found six low-quality case studies or crossover RCTs with a total sample size of 68 patients. A possible benefit of IVIg treatment in these patients was observed, although five studies were not controlled. The Frommer and Madronio (2006) review found one high-quality systematic review (a Cochrane review) of four crossover RCTs with 34 patients. Evidence for improvement in muscle strength with IVIg and limited evidence of a reduction in disability after	The Biotext (2004) review found six low-quality case studies or crossover RCTs with a total sample size of 68 patients. A possible benefit of IVIg treatment in these patients was observed, although five studies were not controlled. The Frommer and Madronio (2006) identified a Cochrane systematic review including four RCTs. Thirty-four patients were randomly assigned to IVIg or placebo. IVIg treatment was superior to placebo in inducing an improvement in muscle	Revised to include 2013 double blind placebo controlled trial and 2014 review of small to moderate un-blinded long term follow up studies. Evidence confirmed that Ig treatment must be given early - waiting for significant disability to develop in MMN is usually associated with irreversible axonal loss and consequently irreversible muscle atrophy. Therefore significant disability should not be required before recommending therapy

	IVIg administration. Consensus statements assert that IVIg is the only safe treatment demonstrated to work in patients with MMN. It is recommended in those who have significant disability. Dose and monitoring is similar to chronic inflammatory demyelinating polyneuropathy. IVIg therapy is usually long term, but the minimum effective dose for each patient should be sought. Plasma exchange and steroids appear to cause a worsening in the condition of patients with MMN with conduction block. Regular maintenance doses of IVIg are needed. The National Guideline Clearinghouse recommends the use of IVIg in the treatment of patients with progressive, symptomatic MMN that has been diagnosed using electrophysiology, ruling out other possible conditions that may not respond to IVIg treatment.	strength. There was a trend (p=0.08) to reduced disability. In 2013 Han et al published a double blind placebo controlled study of IVIG treatment in 44 MMN cases Patients were randomized 1:1 to receive either double-blind treatment with IVIg followed by placebo for 12 weeks each, or the reverse. A significant difference (P = 0•005) in mean maximal grip strength was observed during IVIg treatment (increased 3•75%) compared to placebo (decline 31•4%) (Hahn et al 2013). A further review by Leger 2014 described the results of 4 small to moderate sized unblinded long term follow-up studies of both treated and treatment naïve cases. Improvement was demonstrated in up to 70% of cases in grip strength and MRC scores, confirming that IVIg is the most useful agent for initial and maintenance treatment of MMN Consensus statements assert that IVIg is the only safe treatment demonstrated to be effective in patients with MMN. It is recommended in those who have significant disability. Dose and monitoring is similar to chronic inflammatory demyelinating polyneuropathy. IVIg therapy is usually long term, but the minimum effective dose for each patient should be sought. Plasma exchange and steroids are ineffective and may cause deterioration.	

		Regular maintenance doses of IVIg are needed. The National Guideline Clearinghouse (European Handbook of neurological management. 2nd Ed Vol 1 Oxford (UK); Wiley-Blackwell; 2011; p343-50) recommends IVIg as first-line treatment for definite MMN when disability is sufficient to warrant treatment. A trial of IVIg is not recommended for patients with exclusion criteria, or those without typical clinical or electrophysiologic features, who are likely to have MND.	
Description and Diagnostic Criteria	MMN is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.	MMN is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.	MMN is a very rare and often difficult to diagnose condition. The number of patients with the diagnosis of MMN with CB given for the approval of IVIG who do not actually have the diagnosis, which means IVIg use for the disease is disproportionate to the incidence of the disease. A number of SWG members observe that numerous are patients referred – far more than actually have MMN that have had trials of IVIg or continue IVIg for one of many alternative and often Ig non responsive conditions. SWG acknowledged that it was important to ensure appropriate monitoring and review and so stop treatment if response has not been achieved and disease is progressing.

Diagnosis is required	Patients who have multi focal motor neuropathy, with a typical clinical phenotype, with or without persistent conduction block, as diagnosed by a neurologist.	Yes	By which speciality	Neurologist	Unchanged
Diagnosis must be verified		No	By which speciality		
Exclusion Criteria	Presence of upper motor neuron signs. Significant sensory impairment without an adequate alternative explanation.	Presence of upper motor neuron signs. Marked bulbar involvement Significant sensory impairment without an adequate alternative explanation Diffuse symmetric weakness during the initial weeks.			Additional exclusion criteria were added from the National Guideline Clearinghouse.
Indications	First- line therapy for MMN	First-line and maintenance therapy for MMN. Relapse of MMN Patients within six months of commencement of trial off Immunoglobulin therapy			Maintenance added to first indication. Second indication added to support re-entry of patients that relapse within 6 months commencement of trial off Ig therapy. Second indication encourages prescribers to trial off Ig treatment and test when patients may be in remission by balancing that requirement with an ability to re-treat patients that do relapse once Ig therapy ceased.
Qualifying Criteria	Patients who have multi focal motor neuropathy, with a typical clinical phenotype, with or without persistent conduction block, as diagnosed by a	**First-line and maintenance therapy for MMN.**			The diagnosis should be based on “typical phenotype” with or without clear cut Conduction Block (CB). While CB would usually be present, patients without CB can

	neurologist.	• Multifocal motor neuropathy, with a typical clinical phenotype, usually with persistent motor conduction block AND • Progressive motor weakness is demonstrated in the distribution of individual peripheral nerves AND • Demonstration of disability as measured by the INCAT Score (at least 1 point). **Relapse of MMN Patients following cessation of Immunoglobulin therapy** • Previously stable patient demonstrating a deterioration in motor weakness compared to the level of weakness at the last review while on Ig therapy AND • Demonstration of increased disability as measured by the Adjusted INCAT Score (an increase of at least 1 point) compared to the score at the last review AND • Relapse occurs following cessation of Ig therapy	benefit from and respond to Ig treatment. Describing the clinical phenotype is a hurdle for clinicians to consider and provide description but authorisers are not required to evaluate the description. The data will be available for SWG review in due course and system changes might be considered at that time. (A) As MMN is in the majority of cases very slowly progressive and the majority of treated cases do not dramatically respond to therapy, it was recognised that an approach was required to reflect the motor predominance of the condition. If no conduction block is present, the requirement to demonstrate response at initial review is higher than where conduction block is present. For example, where block is present, stabilisation in symptoms after therapy is sufficient but where there is no conduction block – the patient must have improved at review. The choice of assessment methods was problematic due to the nature of MMN - focal weakness with some muscles becoming 'burned out' and unsuitable to be used for assessment of post Ig therapy response. A description has had to be used to describe the improvement in focal weakness. INCAT was chosen to be consistent with

			other conditions to assess disability. The MRC Sum (12) - does not include distal muscles that are vital in MMN, therefore it was unsuitable. Qualification for relapsed patients is also required e.g. deterioration to be demonstrated compared to previous review status and response
Review Criteria	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. Effectiveness Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by	**First line and maintenance treatment for MMN** IVIg should be used for a maximum of 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 of treatment and annually thereafter. Clinical documentation of efficacy is necessary for continuation of IVIg therapy. **On review of an initial authorisation period** Response to Ig treatment must be demonstrated by objective findings of:	Standard assessment by Adjusted INCAT to measure changes in or stability of disability at initial and continuing review will ensure data is comparable nationally. (A) Literature for the placebo controlled trials of IVIg in MMN was reviewed and the criteria for improvement varied in each case. International expert views were also sought. Review must objectively demonstrate a clinical response within 4 months with the review being performed by a neurologist. All patients that are responders will have demonstrated a benefit after induction plus 3 cycles rather than waiting for 6 cycles or courses. The initial assessment timeframe is reduced from a maximum of 6 months to 4 months (induction plus 3 months or courses). This provides consistency with like conditions eg CIDP. (A)

	objective findings of either: Improvement in functional scores activities of daily living (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; OR Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.	• Improvement in focal motor weakness documented by an increase in MRC Score in previously weak (but not end stage) muscles AND • Improvement in disability as measured by the Adjusted INCAT Score (at least 1 point less than the qualifying score) **On review of a continuing authorisation period** Response to Ig treatment can be demonstrated by objective findings of improvement in or stabilisation of disease. It is acknowledged that very slow deterioration may occur over several years in stable patients. • Improvement in or stabilisation of disability as measured by the Adjusted INCAT Score compared to the previous review score. (Gradual deterioration of 1 point over several years is acceptable.) AND • A trial off Ig therapy should be considered once the patient is stable	At continuing review SWG noted that slow deterioration might be 1 point decrease in MRC over a couple of years as patients will eventually deteriorate. (A) Responses for patients both with and without conduction block have been defined with a higher requirement for demonstration of response in patients without conduction block. SWG recommends that consideration of a trial off Ig treatment at 12 months is required. Patients burnout but do not achieve true 'remission'. Some patients are dramatic responders but others will simply stabilise and stop deteriorating. Consideration should be given to a trial off therapy if patient is not continuing to worsen. If patients are diagnosed late (after 5-6 years) - they may already have considerable axonal loss and a clear response may not be demonstrated at the initial review - they will stabilise. Once patients are stable, a trial off Ig therapy should be considered to test whether 'remission' has been achieved. (A) Stable patients may achieve long term

		Relapse of MMN Patients within six months of commencement of trial off Immunoglobulin therapy IVIg should be used for a maximum of 4 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 of starting treatment and annually thereafter. Clinical documentation of efficacy is necessary for continuation of IVIg therapy. **On review of the initial authorisation period** Response to Ig treatment can be demonstrated by objective findings of: • Patient demonstrates improvement in motor weakness in response to four months of Ig therapy compared to muscle strength at qualifying OR • Improvement in disability as measured by the Adjusted INCAT Score compared to qualifying score after relapse. **On review of a continuing authorisation**	remission which will only be evident if trialled off Ig therapy. An avenue to return to Ig treatment is defined for relapse within 6 months of trial commencement. (A)

		period Response to Ig treatment can be demonstrated by objective findings of: • Patient demonstrates improvement in or stable motor weakness compared to the muscle strength at the previous review OR • Improvement in or stabilisation of disability as measured by the Adjusted INCAT Score compared to the previous review score. (Gradual deterioration of one point over several years is acceptable).	
Dose	Induction: 2 g/kg in 2 to 5 divided doses. Maintenance: 0.4–2 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for the minimum dose to maintain optimal functional status. Dosing above 1 g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information. The aim should be to use the lowest dose	**First-line and maintenance therapy for MMN.** **Induction** - 2 g/kg in 2 to 5 divided doses. **Maintenance** - 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response up to a maximum dose of 2 g/Kg in any 4 week period. This might be given by divided doses more frequently than fortnightly. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products.	SWG noted that there are 2 schools of thought regarding dosing - one is to treat aggressively with 2g/kg and then observe the other is to treat with smaller doses more regularly there are no comparisons of effectiveness and the general feeling is that regular dosing is required not allowing the patient to worsen before retreating is a major goal so that dosing should be aimed at maintaining any functional gains that occur and that dosing should be regularly reviewed. Dosing options will allow more frequent but lower dose or less frequent but higher dose, with the total dose within 1g/kg being

	possible that achieves the appropriate clinical outcome for each patient.	Refer to the current product information sheet for further information. **Relapse of MMN Patients within six months of commencement of trial off Immunoglobulin therapy** **Induction** – 1-2 g/kg in 2 to 5 divided doses. **Maintenance** - 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2 g/Kg may be given in any 4 week period. This might be by divided doses more frequently than fortnightly. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	distributed as clinician prefers. The SWG challenged the minimum dose frequency of 2 weeks as there is no evidence for this. Whereas there is some evidence that low dose weekly therapy is effective (DYCK et al 1994). SWG advised that some clinicians may recommence without the full induction dose so 1-2 g/kg should be allowed rather than a fixed 2g/Kg dose. The SWG confirmed that upper limit of maintenance dosing should be the same as CIDP. The maximum dose for maintenance was reduced from 2g/Kg to 1g/Kg allowing 2g/Kg to be used each month rather than per fortnight. There is no impact from supporting weekly dosing. A range of dose 1-2g/Kg was introduced for induction dose for relapsed patients as clinicians may not always need to use the full 2 g dose.

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