

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 REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative (B) Progressive (C) Programmed
Condition Name	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)	Inflammatory myopathies: inclusion body myositis (IBM)	SWG recommends the separation of IBM from other inflammatory myopathies because the response to treatment and monitoring are quite different for IBM patients compared with other forms of myositis.
Specialty	Neurology	Neurology	
Chapter	5	5	
Specific Conditions	Polymyositis (PM); Dermatomyositis (DM); Inclusion body myositis (IBM)		
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a) for dysphagia Evidence of no probable benefit – more research needed (Category 2b) for muscle weakness	Distinction to be provided between different symptoms of IBM and to indicate that muscle weakness alone is not supported. This was not clear in current version. (A)
Justification for Evidence Category	PM: The Biotext (2004) review included one prospective case-series study of 35 adults with chronic refractory polymyositis. IVIg may be of benefit in these patients, improve mean muscle power and allow reduction in dose of corticosteroid. Further research is needed.	IBM: The Biotext (2004) review identified three small controlled studies. Two were crossover trials comparing intravenous immunoglobulin (IVIg) to placebo in 19 patients and 22 patients. The outcome was negative, even if some symptomatic positive effects were recorded. In one randomized controlled trial (RCT) IVIg plus	Justification for evidence section revised and updated. (A)

	<p>DM: The Biotext (2004) review included one double-blind, placebo-controlled trial considered of low quality of 15 patients with biopsy-confirmed, treatment-resistant dermatomyositis. IVIg treatment combined with prednisone led to significant improvement in muscle strength and neuromuscular symptoms of patients in the intervention group (n=8).</p> <p>IBM: The Biotext (2004) review included three small controlled studies, two of which had a crossover design. A total sample of 77 patients diagnosed with IBM was followed for between 4 and 12 months. The three studies showed possible slight benefit in reducing endomysial inflammation, disease progression and severity of IBM. Further research is needed.</p> <p>One submission reported the effectiveness of IVIg therapy for PM and DM as add-on therapy for patients who have not responded to steroids and immunosuppression (NSW IVIg User Group).</p> <p>A further submission confirms a role for IVIg as add-on maintenance therapy in some patients resulting in an increased chance of complete remission and reduction in corticosteroid dose.</p> <p>A third submission suggests that IVIg can be tried as add-on treatment for patients with PM or DM who have not responded adequately to corticosteroids and second-line immunosuppressive agents (Asia-Pacific IVIg Advisory Board 2004).</p>	<p>prednisolone was compared with placebo plus prednisolone in 35 patients – the outcome was negative. Overall a small number of patients reported benefits regarding swallowing difficulties. IVIg in IBM continues to be controversial. Since there is a question about regional differences in response to IVIg, and persistent case reports about the efficacy of IVIg in IBM, further research is required to determine if a small subset of patients respond. Long-term treatment does not appear justified. However, there may be an exception with regards to treating dysphagia.</p>	
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	Weak evidence suggests that it may benefit patients with dysphagia associated with IBM (Asia–Pacific IVIg Advisory Board 2004).			
Description and Diagnostic Criteria	<p>The inflammatory myopathies are a group of three discrete disorders of skeletal muscle: DM, PM and IBM.</p> <p>These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle.</p> <p>The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists, and relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography and muscle biopsy.</p>	IBM is an idiopathic inflammatory disorder of muscle. It is the most common inflammatory myopathy in individuals older than 50 years. Clinically IBM presents with slowly progressive weakness. It is more common in men than women (3:1). Along with proximal muscle weakness, distal muscles are commonly involved. The disease has a predilection for certain muscles, especially the quadriceps and long finger flexors, with prominent atrophy of the quadriceps muscle.		Diagnostic criteria section has been revised and updated. SWG observed that IVIg in IBM continues to be controversial. Although initial trials looked promising, long term treatment does not appear justified. However there is an exception with regards to treating dysphagia which affects up to 70% IBM patients. This may even apply with the use of subcutaneous IVIg. (Muscle & nerve 2013;48(5):839-9.
Diagnosis is required	Diagnosis made by a neurologist, rheumatologist or immunologist	Yes	By which speciality	Neurologist, rheumatologist or clinical immunologist
Diagnosis must be verified		No	By which speciality	
Exclusion Criteria	Expert consensus does not recommend IVIg to treat the limb weakness of IBM.			IBM with limb weakness without dysphagia affecting function
				This exclusion criterion has been reworded for consistency with other exclusion criteria.
Indications	<p>Patients with PM or DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents.</p> <p>Patients with IBM who have dysphagia affecting</p>			Patients with IBM who have dysphagia limiting dietary intake
				<p>Indication reworded to require biopsy confirmation and clearer definition of degree of dysphagia.</p> <p>SWG confirmed that there is no evidence that can be used to verify rapidly progressive IBM and noted that the criteria</p>

	function. Patients with rapidly progressive IBM.		for rapidly progressive IBM is not clear, and that the indication should be deleted.
Qualifying Criteria	<p>Diagnosis made by a neurologist, rheumatologist or immunologist of:</p> <p>Patients with PM or DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents;</p> <p>OR</p> <p>Patients with IBM who have dysphagia affecting function;</p> <p>OR</p> <p>Patients with rapidly progressive IBM.</p>	<p>Biopsy-proven IBM with dysphagia.</p> <p>AND</p> <p>Dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by videofluoroscopy.</p> <p>AND</p> <p>Patient intolerance for solid dietary textures.</p> <p>OR</p> <p>At least two documented episodes of aspiration for which there is no better explanation.</p>	<p>The qualifying criteria include demonstration of pharyngeal muscular involvement by video fluoroscopy but not be repeated to demonstrate response at review.</p> <p>While it was acknowledged that access to video fluoroscopy is not routine in rural centres, when neurologists review these patients, these investigations can be performed. It was also noted that such investigations have been used in formal IVIg studies.</p> <p>Given that once these patients are prescribed Ig treatment for dysphagia – they are likely to remain on Ig for a long time, so documented evidence should be required.</p> <p>Also, IBM is not that uncommon in the elderly –so there is a need to document the requirement. Food tolerance will be confirmed to be minced, pureed or Liquids food only</p>
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.	IVIg should be used for up to 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.	

	<p>Review</p> <p>Regular review by a neurologist, rheumatologist, or clinical immunologist is required; frequency as determined by clinical status of patient.</p> <p>For stable patients on maintenance treatment, review by a specialist is required at least annually.</p> <p>Effectiveness</p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of either:</p> <p>Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment;</p> <p>OR</p> <p>Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.</p>	<p>Review by a neurologist, rheumatologist, or clinical immunologist is required within four months and annually thereafter.</p> <p>Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.</p> <p>Effectiveness can be demonstrated by objective findings of improvement in dysphagia.</p> <p>On review of an Initial authorisation period</p> <p>Improvement in dysphagia, including as assessed by speech therapist, improvement in dietary intake and aspiration episodes, as relevant.</p> <p>On review of a continuing authorisation period</p> <p>Continued improvement or stabilisation in symptoms of dysphagia, including improvement in speech therapy assessment and improvement in dietary intake or aspiration episodes, as relevant.</p> <p>AND</p> <p>Once stable, a trial off Ig therapy may be considered.</p>	<p>The initial assessment timeframe is reduced from a maximum of 6 months to 4 months (induction plus 3 months or courses).</p> <p>Clear definition of demonstrated response to Ig therapy is defined for re-authorisation. (A)</p> <p>Continued improvement or stabilisation in symptoms. Once stable, a trial off therapy is prompted to be considered. (B)</p> <p>SWG noted that these patients do not go into remission, so are unlikely to cease IVIg if it has been effective. SWG confirmed that it was reasonable to consider trial but should not be mandated and no justification is required.</p>
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<p>Dose</p>	<p>Induction: 2 g/kg in 2 to 5 divided doses. Maintenance: 0.4–1 g/kg, 4–6 weekly.</p> <p>Aim for the minimum dose to maintain optimal functional status.</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>	<p>Induction - 2 g/kg in 2 to 5 divided doses. Maintenance - 0.4–1 g/kg, 4–6 weekly</p> <p>A maximum total dose of 1g/kg may be given in any four week period. This can be administered in weekly divided doses, provided total maximum is not exceeded.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p>	<p>Dosing unchanged however has been notation added that weekly doses can be supported provided that the total maximum dose is not exceeded.</p>
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BIBLIOGRAPHY

- Association of British Neurologists 2005, *Guidelines for the use of intravenous immunoglobulin in neurological diseases*, The Association, London. Available from: www.theabn.org/abn/userfiles/file/IVIg-guidelines-final-July05.pdf. [cited 7 Dec 2007]
- Cherin, P, Pelletier, S, Teixeira, A, et al 2002, 'Results and long-term follow up of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients', *Arthritis & Rheumatism*, vol. 46, no. 2, pp. 467–74.
- Choy, EHS, Hoogendijk, JE, Lecky, B, et al 2005, 'Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Cochrane Review)', in *The Cochrane Library*, Issue 3, John Wiley & Sons, Ltd, Chichester, UK.
- Dalakas, MC 2004, 'The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile', *Pharmacology & Therapeutics*, vol. 102, no. 3, pp. 177–93.
- Dalakas, MC 2005, 'Polymyositis, dermatomyositis, and inclusion body myositis', in DL Kasper, E Braunwald, AS Fauci, et al (eds), *Harrison's Textbook of Medicine*, 16th edn, McGraw-Hill, New York, pp. 2540–45.
- Dalakas, MC, Illa, I, Dambrosia, JM, et al 1993, 'A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis', *New England Journal of Medicine*, vol. 329, no. 27, pp. 1993–2000.
- Dalakas, MC, Koffman, B, Fujii, M, et al 2001, 'A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM', *Neurology*, vol. 56, no. 3, pp. 323–7.
- Dalakas, MC, Sonies, B, Dambrosia, J, et al 1997, 'Treatment of inclusion body myositis with IVIg: a double-blind, placebo-controlled study', *Neurology*, vol. 48, no. 3, pp. 712–6.

Kornberg, AJ, for the Asia–Pacific IVIg Advisory Board 2004, *Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology*, 1st edn, Asia–Pacific IVIg Advisory Board, Melbourne.

Walter, MC, Lochmuller, H, Toepfer, M, et al 2000, 'High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study', *Journal of Neurology*, vol. 247, no. 1, pp. 22–8.

Wiles, CM, Brown, P, Chapel, H, et al 2002, 'Intravenous immunoglobulin in neurological disease: a specialist review', *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 72, no. 4, pp. 440–8.

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