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: polymyositis (PM), dermatomyositis (DM) and necrotising autoimmune myopathy (NAM)**	Inflammatory Myopathies have been split into 2 conditions - Inclusion Body Myositis as a separate condition from Polymyositis (PM) and Dermatomyositis (DM). This is because the criteria and evidence for IBM is different from PM/DM. SWG recommends that Necrotising Autoimmune Myopathy (NAM) that has been a subset of Polymyositis diagnostically but is now becoming recognised as a separate diagnostic entity as scientific knowledge improves. It was agreed that the capacity to use Ig should not be ceased and demand will not change by identifying these patients as a separate group. The number of patients is relatively small but should be tracked in data. SWG noted that NAM has a different level of evidence and agreed that it should be represented as a specific condition within the PM/DM Condition. (A)

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
Specialty	Neurology	Neurology	
Chapter	5	5	
Specific Conditions	Polymyositis (PM); Dermatomyositis (DM); Inclusion body myositis (IBM)	Polymyositis (PM) Dermatomyositis (DM) Necrotising autoimmune myopathy (NAM)	
Level of Evidence	Evidence of probable benefit (Category 2a).	PM and DM – Evidence of probable benefit (Category 2a). NAM – Small case studies only, insufficient data (Category 4a)	Level of evidence was confirmed for all specific conditions.
Description and Diagnostic Criteria	The inflammatory myopathies are a group of three discrete disorders of skeletal muscle: DM, PM and IBM. These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle. The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists, and	Dermatomyositis and polymyositis are idiopathic inflammatory myopathies. Necrotizing autoimmune myopathy typically has necrotic myofibres with less inflammatory infiltrate and the absence of direct myocyte invasion by lymphocytes. These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle. The weakness usually develops subacutely but may be chronic and present over many months. Proximal muscles are predominantly affected in a symmetric fashion.	Diagnostic criteria have been revised and updated including NAM. Feedback from public consultation has confirmed the different approach applied in the diagnosis of children and therefore a separate indication has been developed due to the different qualifying criteria. (A)

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
	relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography and muscle biopsy.	In adults, the diagnosis of DM, PM and NAM relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography and muscle biopsy. . In children, the combination of a characteristic rash, raised muscle enzymes, an objective measure of muscle weakness e.g. Childhood Myositis Assessment Scale (CMAS) and typical MRI scan abnormalities are considered sufficient for diagnosis, with muscle biopsy reserved for atypical cases. NAM is often associated with a history of statin exposure, and the presence of autoantibodies against HMG coenzyme reductase, or other muscle antigens.	
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.	PM: The Biotext (2004) review identified one prospective case-series study of 35 adults with chronic refractory polymyositis. This study reported clinical improvement in 71% of patients with significant improvement in muscle power, muscle disability scores and CK levels ($p < 0.01$). Steroid dose could be reduced after IVIg ($p < 0.05$). Further research is needed.	Justification for evidence revised and updated (A)

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
	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). 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. One submission reported the effectiveness of IVIg therapy for PM and DM as add-on therapy for patients who have not	DM: The Biotext (2004) review identified 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). One retrospective chart review and two case series tried IVIg as add on therapy (Class III evidence). Taken together, 82% improved clinically in these studies. NAM: Patients with NAM were likely to have previously been regarded as having PM, increasingly this is being recognised as a separate entity. Small-case series consistently report improvement with immunosuppressive therapy. Often multiple immunotherapeutic agents are required. High-dose steroids are the mainstay of therapy, with IVIg required for some months as rescue therapy in some patients, until other immunosuppressive agents become effective. No trials of IVIg or prospective series have been conducted in NAM. Further research is needed.	

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
	responded to steroids and immunosuppression (NSW IVIg User Group). 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. 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). Weak evidence suggests that it may benefit patients with dysphagia associated with IBM (Asia–Pacific IVIg Advisory Board 2004).				
Diagnosis is required	Diagnosis made by a neurologist, rheumatologist or immunologist	Yes	By which speciality	Neurologist, Rheumatologist or Clinical Immunologist	Unchanged.

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
Diagnosis must be verified		No	By which speciality		
Exclusion Criteria	Expert consensus does not recommend IVIg to treat the limb weakness of IBM.				Exclusion criteria has been deleted.
Indications	Patients with PM or DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents. Patients with IBM who have dysphagia affecting function. Patients with rapidly progressive IBM.	**Adults with biopsy-proven PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant agents.** **Children with clinical, biochemical and imaging abnormalities consistent with definite PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant agents.**			Indication is qualified to note the requirement for muscle biopsy. SWG reported that there is a small subset of patients in whom dysphagia worsens following the introduction of steroids, despite improvement in limb weakness, who may require 3-6 months of IVIg for resolution of the dysphagia. Separate indication for children added.
Qualifying Criteria	Diagnosis made by a neurologist, rheumatologist or immunologist of:	**Adults with biopsy-proven PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and other**			The MRC Sum (12) Score will be used to assess muscle weakness and determine response at review. Video-fluoroscopy will

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
	Patients with PM or DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents; OR Patients with IBM who have dysphagia affecting function; OR Patients with rapidly progressive IBM	**immunosuppressant agents.** **[Group 1]** • Patients with biopsy-proven PM, DM or NAM AND [Group 2] • Significant muscle weakness as measured by Medical Research Council (MRC) Sum (12) Score to a value of less than 56 points. OR • Significant dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by video-fluoroscopy unless speech pathology assessment indicates that video fluoroscopy in the particular patient is associated with an unacceptable risk of aspiration. AND **[Group 3]** • Patient has not responded to corticosteroid	be used to demonstrate the involvement of pharyngeal muscles. SWG considered the application of disability scales at length - however, there is no commonly used or validated disability scale that can be practically used in the clinic setting for PM/DM– all those identified in the literature are research based and too time consuming for use in outpatient clinics. Amendment to criteria where patient risk of aspiration from video fluoroscopy is assessed as being unacceptable.

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
		treatment OR • Corticosteroids are contraindicated AND [Group 4] • At least two other immunosuppressant medications have been used and are ineffective or have been commenced but not yet become effective. OR • Immunosuppressant medications are contraindicated. **Children with clinical, biochemical and imaging abnormalities consistent with definite PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant agents.** • Patient demonstrates at least three of the following characteristics: characteristic rash;	Immunosuppressant agents that are alternative therapies are: • Azathioprine • Methotrexate • Cyclophosphamide • Chlorambucil • Cyclosporin A SWG noted that when PM/DM very acute and severe – Ig is likely to be used in the early phase of the disease while immunosuppressant medications are still taking effect. This has been accommodated in the qualifying criteria. New indication for children with relevant diagnostic criteria and CMAS as the assessment method.

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
		elevated muscle enzymes; typical MRI scan abnormalities or diagnostic muscle biopsy. AND • Significant muscle weakness as measured by the Childhood Myositis Assessment Scale (CMAS) to a value of less than 45 points or significant dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by video-fluoroscopy unless speech pathology assessment indicates that a video fluoroscopy procedure would carry significant risk to the patient. AND • Patient has not responded to corticosteroid treatment unless corticosteroids are contraindicated AND • At least two immunosuppressant agents have been used and are ineffective or have been commenced but not yet become	

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
		effective unless immunosuppressant medication is contraindicated.	
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. **Review** Regular review by a neurologist, rheumatologist, or clinical immunologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a specialist is required at least annually. Effectiveness Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.	**Adults with biopsy-proven PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant agents.** IVIg should be used for up to 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, Rheumatologist, or Clinical Immunologist is required; within four months and annually thereafter. Documentation of clinical efficacy is necessary for continuation of Ig therapy. Efficacy can be demonstrated by objective findings of: • Improvement in muscle weakness • Improvement in dysphagia	Cessation to be considered at 4 months at initial review and then 12 monthly at annual review once stable or when alternative immunosuppressant agents have been commenced..

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
	Effectiveness can be demonstrated by objective findings of either: Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 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.	**On review of an Initial authorisation period** • Patient demonstrating improvement in muscle weakness as assessed by an increase in MRC Sum (12) Score (compared to qualifying score). OR • Patient with improvement in dysphagia as assessed by speech pathology, tolerance of food textures and/or reduced episodes of aspiration **On review of a continuing authorisation period** • Patient demonstrating stabilisation or improvement in muscle weakness as measured by MRC Sum (12) Score (greater than or equal to the previous review score). OR • Patient demonstrating stabilisation or improvement in dysphagia as assessed by speech therapy, improved tolerance	Review criteria were discussed and SWG agreed that there was insufficient data available to be prescriptive on specific improvement levels for response. The review score must be greater than the qualifying score.

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
		of food texture and/or reduced episodes of aspiration AND • A trial off Ig therapy is planned or a valid reason is provided as to what a trial is not being planned or is contraindicated at this time. For stable patients on maintenance treatment, review by a specialist is required at least annually. Most patients do not require long term therapy and progressive reduction in dosing should be considered. Cessation of Ig therapy should be considered once alternative immunomodulating agents have been commenced and are effective and the patient is stable. **Children with clinical, biochemical and imaging abnormalities consistent with definite PM or DM or NAM who have significant muscle weakness or dysphagia unresponsive to corticosteroids and**	Script added noting that long term therapy is not required and progressive reduction in dosing should be considered. Review for children including CMAS as the assessment method.

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
		other immunosuppressant agents. 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. Review by a Paediatric Neurologist, Rheumatologist, or Clinical Immunologist is required within four months and annually thereafter. Documentation of clinical efficacy is necessary for continuation of Ig therapy. Efficacy can be demonstrated by objective findings of: • improvement in muscle weakness • improvement in dysphagia. **On review of an initial authorisation period** Patient demonstrating improvement in muscle weakness as assessed by an increase in CMAS compared to qualifying score by at least 2 points. OR Patient with improvement in dysphagia as assessed by speech pathology, tolerance of food textures	

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
		and/or reduced episodes of aspiration. **On review of a continuing authorisation period** Patient demonstrating stabilisation or improvement in muscle weakness as measured by CMAS greater than or equal to the previous review score OR Patient demonstrating stabilisation or improvement in dysphagia as assessed by speech therapy, improved tolerance of food texture and/or reduced episodes of aspiration. **AND** A trial off Ig therapy is planned and if not planned, a valid reason is provided. For stable patients on maintenance treatment, review by a specialist is required at least annually. Most patients do not require long term therapy and progressive reduction in dosing should be considered. Cessation of Ig therapy should be considered once alternative immunomodulating agents have been	

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
		commenced and are effective and the patient is stable.	
Dose	Induction: 2 g/kg in 2 to 5 divided doses. Maintenance: 0.4–1 g/kg, 4–6 weekly. 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 possible that achieves the appropriate clinical outcome for each patient.	**Induction** - 2 g/kg in 2 to 5 divided doses. **Maintenance** 0.4–1 g/kg, 4–6 weekly A maximum total dose of 1g/kg may be given in any four week period. This can be administered in weekly divided doses, provided the total maximum is not exceeded Induction dose can be given only once, unless treatment has been ceased and re-treatment is required at a later date. Most patients do not require long term therapy and progressive reduction in dosing should be considered. Cessation of Ig therapy should be considered once alternative immunomodulating agents have been commenced and are effective and the patient is stable. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	Total dosing unchanged however script added - A maximum total dose of 1g/kg may be given in any 4 week period. This can be administered in weekly divided doses, provided the total maximum is not exceeded. (A)

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
		Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	

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', 7, 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 Neurolology*, 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.

END OF DOCUMENT