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	Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis (ADEM)	
Specialty	Neurology	Neurology	
Chapter	6	6	
Specific Conditions		Monophasic ADEM Recurrent ADEM Multiphasic ADEM	
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a)	
Justification for Evidence Category	On review of multiple case series of IVIg use for paediatric ADEM found that children with monophasic ADEM completely recovered after administration of IVIg or IVIg plus corticosteroids. In recurrent ADEM, children either completely recovered after IVIg, or showed improvement. Adults with monophasic or recurrent ADEM recovered after treatment with IVIg.	On review of multiple case series of intravenous immunoglobulin (IVIg) use for paediatric ADEM found that children with monophasic ADEM completely recovered after administration of IVIg or IVIg plus corticosteroids. In recurrent ADEM, children either completely recovered after IVIg, or showed improvement. Adults with monophasic or recurrent ADEM recovered after treatment with IVIg. Data from the International Paediatric MS Study Group (IPMSSG) in 2014 confirms this view.	Revised with addition from the IPMSSG (International Paediatric MS Study Group) in 2014 confirms category 2a.
Description and Diagnostic Criteria	High-dose corticosteroids are first-line treatment of ADEM. IVIg has been used for patients who fail to respond to steroid therapy or in patients where steroids are contraindicated. Most patients with ADEM recover completely over a period of six	ADEM is a monophasic inflammatory condition of the central nervous system that usually presents in children and young adults. It typically occurs following a viral prodrome with multifocal neurological disturbance and altered conscious	Revised to describe and require IPMSSG Criteria to be used.

	weeks from onset. There is no biological marker for ADEM. Diagnosis is by clinical recognition of the multifocal neurological disturbance and altered conscious state, with the typical MRI findings of demyelination.	state. ADEM usually follows a monophasic course, but patients may experience recurrence of the initial symptom complex (recurrent ADEM) or a second episode of ADEM (multiphasic ADEM). The majority make a full recovery. ADEM is thought to have an autoimmune basis. Pathologic similarities to experimental allergic encephalomyelitis (EAE), an animal model of inflammatory demyelination, support this theory. It is postulated that a common antigen shared by an infectious agent and a myelin epitope results in an autoimmune response. Patients show multiple demyelinating lesions on magnetic resonance imaging (MRI) in the deep and subcortical white matter. The differential diagnosis includes other inflammatory demyelinating disorders, such as multiple sclerosis, optic neuritis and transverse myelitis. High-dose corticosteroids are first-line treatment of ADEM. IVIg has been used for patients who fail to respond to steroid therapy or in patients where steroids are contraindicated. Most patients with ADEM recover completely over a period of six weeks from onset. There is no biological marker for ADEM. Diagnosis is by clinical recognition of the multifocal neurological disturbance and altered conscious state, with the typical MRI findings of demyelination. The IPMSSG criteria must be used for diagnosis.	

		Krupp, LB, Tardieu, M, Amato, MP, et al 2013, 'International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions', *Multiple Sclerosis Journal*, vol. 19, pp. 1261–1267.			
Diagnosis is required	**Note**: Assessment by a neurologist is recommended, but not mandatory.	Yes	**By which speciality**	Neurologist	Now limited to Neurologists.
Diagnosis must be verified		No	**By which speciality**		
Exclusion Criteria					
Indications	ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated.	Monophasic ADEM unresponsive to steroid therapy or where steroids are contraindicated. Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory. Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy.			Additional indication to support patient re-entry where relapse occurs within 6 months of trial off therapy.
Qualifying Criteria	ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). **Note**: Assessment by a neurologist is recommended, but not mandatory.	**ADEM unresponsive to steroid therapy or where steroids are contraindicated.** • Diagnosis of ADEM consistent with IPMSSG criteria (confirmed on magnetic resonance imaging [MRI]) with recurrent symptoms arising from demyelination.			SWG agreed that Monophasic ADEM Treatment is usually 4-6 weeks. IN some instances, up to three months treatment can be required. At 3 months there should be no new lesions with the patient getting better.

	OR Recurrent or multiphasic ADEM unresponsive to steroid therapy, or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.	AND • No clinical response has been achieved following standard steroid therapy or steroid therapy is contraindicated. Up to three doses may be requested where monophasic ADEM is extended and symptoms do not respond to a first treatment. After three months, an alternative diagnosis should be considered. **Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.** • Diagnosis of recurrent or multiphasic ADEM (as per IPMSSG criteria) (Krupp et al. 2013). AND • No clinical response has been achieved following standard steroid therapy or steroid therapy is contraindicated or intolerable. **Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy.** • Diagnosis of recurrent or multiphasic ADEM	Recurrent ADEM will have different new lesions – the patient would be eligible for further treatment under the other indication. Multi-phasic has a grumbling course with different lesions and symptoms. Criteria extended to require diagnosis to be MRI proven and patient to have a failed clinical response to steroids or stated contraindication reason IPMSSG criteria are found in: [1]Krupp, LB, Tardieu, M, Amato, MP, et al 2013, 'International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions', *Multiple Sclerosis Journal*, vol. 19, pp. 1261–1267.

		(as per IPMSSG criteria) (Krupp et al. 2013). AND • Evidence of deterioration in symptoms AND • Relapse occurs within six months of the last immunoglobulin (Ig) dose.	
Review Criteria		**Monophasic ADEM unresponsive to steroid therapy or where steroids are contraindicated.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. The review is for the purpose of gathering objective evidence of improvement as a result of Ig treatment: • Improvement in relapse rate in comparison to pre-treatment levels **Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.** Review by a neurologist is required every six months for recurrent or multiphasic ADEM. Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective	Response must be demonstrated after 6 months treatment for re-authorisation. Trial off therapy must be undertaken after 12 months treatment. If patients with Recurrent or Multi-phasic ADEM relapse within 6 months of ceasing Ig treatment, re-entry is defined with requirement for further response at review.

	Objective evidence of improvement in relapse rate in comparison to pre-treatment levels. Six-monthly review by a neurologist is required for recurrent or multiphasic ADEM.	findings of improvement in relapse rate in comparison to pre-treatment levels. **On review of an initial authorisation period** • After six months Ig treatment, patient demonstrates improvement in ADEM symptoms, including no new lesions on MRI and a stabilised clinical course, are eligible for a further six months of treatment. **(No continuing review is required)** After that time, a trial off Ig therapy should be commenced. If the patient relapses within six months of ceasing (with clinical and radiological evidence of relapse), patients may qualify under that indication. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. **Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off Immunoglobulin therapy.** Review by a neurologist is required every six months for recurrent or multiphasic ADEM. Clinical documentation of effectiveness is necessary for continuation of IVIg therapy.	

		Effectiveness can be demonstrated by objective findings of improvement in relapse rate in comparison to pre-treatment levels. **On review of an initial authorisation period** • After 6 months Ig treatment, patients demonstrate improvement in ADEM symptoms including no new lesions on MRI and stabilised clinical course. **On review of a continuing authorisation period** • Patients demonstrate improvement in ADEM symptoms, including no new lesions on MRI and stabilised clinical course. AND • A trial off Ig therapy is planned or a valid reason provided as to why a trial is not being planned.	SWG confirmed that treatment cessation should be considered at 12 months. If the patient relapses, (with clinical and radiological evidence of relapse), re-entry should be supported. SWG advised that even relapsed patients should not remain on Ig indefinitely. Cessation should be considered annually with weaning off therapy and a trial off therapy.
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance dose:** For recurrent or multiphasic ADEM only: 0.4–2 g/kg, 4–6 weekly. Aim for the minimum dose to maintain optimal functional status and prevent relapses. In recurrent or multiphasic ADEM, assessment by a neurologist is **mandatory**. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.**	**Monophasic ADEM unresponsive to steroid therapy or where steroids are contraindicated** **Induction Dose** - Up to 2 g/kg in 2 to 5 divided doses. **Maintenance Dose -** For extended monophasic ADEM: 0.4–2 g/kg, 4-–6 weekly. Up to three doses (induction + two maintenance	Monophasic is usually treated by a one off dose but the underlying disease may continue for 3 months – therefore treatment may need to continue for 3/12. Up to 2 additional doses (maintenance) can be requested. If further treatment is needed, then an alternate diagnosis and review is

	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.**	doses) may be used for extended monophasic ADEM. After three months, if symptoms persist, an alternative diagnosis should be considered**.** 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.** **Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.** **Induction -** Up to 2 g/kg in 2 to 5 divided doses kg as a single dose. **Maintenance -** For recurrent or multiphasic ADEM: 0.4–2 g/kg, 4–6 weekly. 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.	mandatory.

		Refer to the current product information sheet for further information. **Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy.** **Induction -** Up to 2 g /kg in 2–5 divided doses. **Maintenance -**For recurrent or multiphasic ADEM: 0.4–2 g/kg, 4–6 weekly. 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.**	

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