Acute disseminated encephalomyelitis (ADEM)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Monophasic acute disseminated encephalomyelitis (ADEM) • Recurrent acute disseminated encephalomyelitis (ADEM) • Multiphasic acute disseminated encephalomyelitis (ADEM)
Indication for IVIg Use	• Monophasic ADEM unresponsive to corticosteroid therapy or where corticosteroids are contraindicated • Recurrent or multiphasic ADEM unresponsive to steroid therapy or where corticosteroid therapy has become intolerable or is contraindicated • Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Acute disseminated encephalomyelitis (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 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. Intravenous immunoglobulin (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 International Paediatric MS Study Group (IPMSSG) criteria must be used for diagnosis (Krupp, LB, Tardieu, M, Amato, MP, et al 2013).
Justification for Evidence Category	On review of multiple case series of intravenous immunoglobulin (IVIg) use for paediatric acute disseminated encephalomyelitis (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 Pediatric MS Study Group (IPMSSG) in 2014 confirms this view.
Diagnosis Requirements	A diagnosis must be made by a Neurologist.

Qualifying Criteria for IVIg Therapy

Monophasic ADEM unresponsive to corticosteroid therapy or where corticosteroids are contraindicated

- Diagnosis of acute disseminated encephalomyelitis (ADEM) consistent with International Paediatric MS Study Group (IPMSSG) criteria (encephalopathy, polyfocal deficits plus confirmed magnetic resonance imaging [MRI] compatible with demyelination) with ongoing symptoms arising from demyelination

AND

- Unresponsive to standard corticosteroid therapy

  OR
- Corticosteroid therapy has resulted in unacceptable side effects or significant toxicity

  OR
- Corticosteroid 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 and/or therapy should be considered.

Recurrent or multiphasic ADEM unresponsive to steroid therapy or where corticosteroid therapy has become intolerable or is contraindicated

This indication is for patients with **recurrent or multiphasic ADEM**, if patients relapse within six months of cessation of Ig therapy, an application can be submitted under the indication: **Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy**.

- Diagnosis of recurrent or multiphasic acute disseminated encephalomyelitis (ADEM) (as per International Paediatric MS Study Group (IPMSSG) criteria) (Krupp et al. 2013)

AND

- Unresponsive to standard corticosteroid therapy

  OR
- Corticosteroid therapy has resulted in unacceptable side effects of significant toxicity

  OR
- Steroid therapy is contraindicated

A maximum of 12 months treatment is permitted under this indication. Review by a neurologist is required at six months to assess response to therapy.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy

ADEM patients with clinical and radiological evidence of relapse within six months of ceasing Ig therapy may qualify under this indication.

Where a relapse event does occur, a diagnosis of multiple sclerosis (MS) or neuromyelitis optica spectrum disorder should also be considered and MS disease modifying therapies or other therapies considered.

- Diagnosis of recurrent or multiphasic acute disseminated encephalomyelitis (ADEM) (as per IPMSSG criteria) (Krupp et al. 2013)

  AND

- Deterioration in symptoms following cessation of Ig therapy

  AND

- Relapse occurs within six months of the last immunoglobulin (Ig) dose

IVIg should be used for a maximum period of six months (induction plus five 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 every six months.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Review Criteria for Assessing the Effectiveness of IVIg Use

Monophasic ADEM unresponsive to corticosteroid therapy or where corticosteroids are contraindicated

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.

- Clinical improvement in and stabilisation of symptoms in comparison to pre-treatment levels

Recurrent or multiphasic ADEM unresponsive to steroid therapy or where corticosteroid therapy has become intolerable or is contraindicated

A maximum of 12 months treatment is permitted under this indication. Review by a neurologist is required at six months to assess response to therapy.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Improvement in ADEM symptoms, including no new lesions on MRI and stabilised clinical course after six months Ig treatment

On review of a continuing authorisation period

- Improvement in ADEM symptoms, including no new lesions on magnetic resonance imaging (MRI) and stabilised clinical course after six months of Ig treatment

After six months treatment, patients demonstrating improvement in ADEM symptoms, including no new lesions on MRI and a stabilised clinical course, are eligible for one further authorisation for a maximum of a further six months of treatment (i.e. 12 months Ig treatment in total). After that time, a trial off Ig therapy is required.

If the patient relapses within six months of ceasing Ig therapy (with clinical and radiological evidence of relapse), patients may qualify under the indication **Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy.**

Where a relapse event does occur, a diagnosis of multiple sclerosis (MS) or neuromyelitis optica spectrum disorder should also be considered and MS disease modifying therapies or other therapies considered.

Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy

IVIg should be used for a maximum period of six months (induction plus five 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 every six months.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Improvement in ADEM symptoms including no new lesions on MRI and stabilised clinical course in comparison to pre-treatment levels

On review of a continuing authorisation period

- Improvement in multiphasic acute disseminated encephalomyelitis (ADEM) symptoms, including no new lesions on MRI and stablised clinical course in comparison to previous review assessment

  AND

- A trial of weaning/cessation of Ig therapy is planned or a valid reason provided as to why a trial is not being planned or is contraindicated at this time

Dose

Monophasic ADEM unresponsive to corticosteroid therapy or where corticosteroids are contraindicated

- **Induction Dose** - up to 2 g/kg in 2 to 5 divided doses.
- **Follow-up Dose** - 1 g/kg followed by a second dose (if required) after 4 to 6 weeks for extended monophasic ADEM.

Up to three doses (induction plus up to two follow-up doses) may be used for extended monophasic ADEM. After three months, if symptoms persist, an alternative diagnosis or therapy should be considered.

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 on dose, administration and contraindications.

Recurrent or multiphasic ADEM unresponsive to steroid therapy or where corticosteroid therapy has become intolerable or is contraindicated

- **Induction Dose** - 2 g/kg in 2 to 5 divided doses.
- **Maintenance Dose** - 1 g/ kg 4–6 weekly.

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 on dose, administration and contraindications.

Relapse of patients with recurrent or multiphasic ADEM within six months of commencement of trial off immunoglobulin therapy

- **Induction Dose** - Up to 2 g/kg in 2–5 divided doses.
- **Maintenance Dose** - 1 g/kg, 4–6 weekly.

Aim for the minimum dose to maintain optimal functional status and prevent relapses.

Refer to the current product information sheet for further information on dose, administration and contraindications.ions.

Bibliography

Andersen, JB, Rasmussen, LH, Herning, M, et al 2001, 'Dramatic improvement of severe acute disseminated encephalomyelitis after treatment with intravenous immunoglobulin in a three-year-old boy', *Developmental Medicine & Child Neurology*, vol. 43, no. 2, pp. 136–8.

Feasby, T, Banwell, B, Benstead, T, et al 2007, 'Guidelines on the use of intravenous immune globulin for neurologic conditions', *Transfusion Medicine Reviews, vol.* 2, no. 2:S1, pp. S57–107. http://www.sciencedirect.com/science/article/pii/S088779630700003X

Finsterer, J, Grass, R, Stollberger, C, et al 1998, 'Immunoglobulins in acute, parainfectious, disseminated encephalomyelitis', *Clinical Neuropharmacology*, vol. 21, pp. 258–61.

Hahn, JS, Siegler, DJ and Enzmann, D, 1996, 'Intravenous gammaglobulin therapy in recurrent acute disseminated encephalomyelitis', *Neurology*, vol. 46, no. 4, pp. 1173–4. https://www.ncbi.nlm.nih.gov/pubmed/8780119

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

Bibliography

definitions', *Multiple Sclerosis Journal*, vol. 19, pp. 1261–1267. https://www.ncbi.nlm.nih.gov/pubmed/23572237

Kleiman, M and Brunquell, P, 1995, 'Acute disseminated encephalomyelitis: response to intravenous immunoglobulin?', *Journal of Child Neurology*, vol. 10, no. 6, pp. 481–3. http://journals.sagepub.com/doi/pdf/10.1177/088307389501000612

Marchioni, E, Marinou-Aktipi, K, Uggetti, C, et al 2002, 'Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis', *Journal of Neurology, vol.* 249, no. 1,pp. 100–4. https://www.ncbi.nlm.nih.gov/pubmed/11954856

Mariotti, P, Batocchi, AP, Colosimo, C, et al 2003, 'Multiphasic demyelinating disease involving central and peripheral nervous system in a child', *Neurology*, vol 60, no. 2, pp. 348–9. http://www.neurology.org/content/60/2/348.short

Nishikawa, M, Ichiyama, T, Hayashi, T, et al 1999, 'Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis', *Paediatric Neurology*, vol. 21, no. 2, pp. 583–6. http://www.sciencedirect.com/science/article/pii/S0887899499000429

Pittock, SJ, Keir, G, Alexander, M, et al 2001, 'Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis; *European Journal of Neurology*, vol. 8, no. 6, pp. 725. http://onlinelibrary.wiley.com/doi/10.1046/j.1468-1331.2001.00195.x/abstract

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