Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens (AMAE)

Condition for which Ig has an emerging therapeutic role.

Specific Conditions	• Encephalitis associated with antibodies to NMDA receptor • Encephalitis associated with antibodies to VGKC • Encephalitis associated with antibodies to LGI1 • Encephalitis associated with antibodies to CASPR2 • Encephalitis associated with antibodies to DPPX • Encephalitis associated with antibodies to AMPA receptor • Encephalitis associated with antibodies to glycine receptor • Encephalitis associated with antibodies to GABA (A or B) receptor • Suspected autoimmune encephalitis • Sero-negative autoimmune encephalitis • Suspected autoimmune limbic encephalitis • Sero-negative limbic encephalitis
Indication for Ig Use	• Confirmed antibody mediated autoimmune encephalitis (AMAE) or limbic encephalitis – cell surface antibody positive • Suspected antibody mediated autoimmune encephalitis (AMAE) – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis is an antibody mediated neurological disease initially described in 2005. It is the most common and best described of the encephalitides associated with antibodies to neuronal cell surface antigens. There is compelling evidence suggesting the role for IgG1 and IgG2 antibodies in binding to the GluN1 subunit of the NMDA-receptor. A proportion of cases are associated with underlying teratomas and tumour removal may be curative. A probable diagnosis can be made (Graus et al, 2016) when all three of the following criteria have been met: 1. Rapid onset (less than three months) of at least four symptom groups including: • Abnormal (psychiatric) behaviour or cognitive dysfunction • Speech dysfunction (pressured speech, verbal reduction, mutism) • Seizures • Movement disorder, dykinesias or rigidity/ abnormal postures • Decreased level of consciousness • Autonomic dysfunction or central hypoventilation 2. At least one of the following laboratory study results: • Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity or extreme delta brush) • CSF with pleocytosis or oligoclonal bands 3. Reasonable exclusion of other disorders. Diagnosis can also be made in the presence of three of the above symptom groups accompanied by a systemic teratoma. A definite diagnosis can be made in the presence of one or more of the six major symptom groups and IgG anti-GluN1 antibodies after reasonable exclusion of other disorders. Treatment thus consists of immunotherapy and tumour resection. First line immunotherapy typically includes intravenous methylprednisolone and IVIg or plasmapheresis. Due to the behavioural and/or autonomic manifestations of the disease, plasmapheresis, with large bore catheters may be clinically inappropriate. Second line treatment includes rituximab and cyclophosphamide. The consensus opinion is that one would progress to the addition of second line treatment in a standard case if no clinical improvement is observed after approximately two weeks of first line therapy and no tumour is found. There are a variety of rarer neuroimmunological syndromes for which there is good evidence of antibodies binding physiologically relevant neuronal surface antigens with a case literature describing responses to immunotherapy often including IVIG. All these syndromes have both distinctive clinical features described matching particular antibodies but also have some cases described where there is clinical overlap with those associated with other antoibodies or other CNS inflammatory disorders. In many of these syndromes

associations with malignancies have been identified and clinicians treating such cases should be familiar with the literature and investigate accordingly.

Some cases also have more than one antibody identified.

Rare cases occur in which an infectious trigger is identified. Herpes simplex virus encephalitis induced anti-NMDAR encephalitis is an autoimmune process and immune responsive condition which has a 50 percent mortality in children and immune suppression and modulation (steroid, ivig, rituximab) have a role (Armangue et al, 2015).

VGKC-Abs has been described in heterogeneous disorders such as limbic encephalitis or Isaac and Morvan syndromes. The antibodies bind associated proteins such as Lgi1 (limbic encephalitis) and Caspr2 (neuromyotonia) rather than the VGKC itself in almost all cases. An associated tumor is observed rarely in patients with Lgi1 Ab and less than 30 percent patients with Caspr2 Ab. A different potassium channel associated protein DPPX has also been described.

Limbic encephalitis and other clinical encephalitis syndromes can occur with alternate antibodies directed against cell surface synaptic antigens (AMPAr, GABAa, GABAb, glycine).

Testing may not be available within Australia for all relevant antibodies. Testing CSF in addition to serum has a higher yield than serum alone and should be performed ab initio on both serum and CSF unless there are strong reasons to avoid lumbar puncture.

The term Hashimoto's encephalopathy has been previously used to describe acquired acute or subacute encephalopathy in patients with autoimmune thyroid disease. This syndrome is immune responsive and also called steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT). It is generally agreed that the anti-thyroid antibodies do not cause the brain disease, but instead represent an 'autoimmune predisposition' in these individuals. It should also be noted that the presence of anti-thyroid antibodies alone is not diagnostic of autoimmune disease, as these antibodies are seen in well individuals with a family history of thyroid or related autoimmunity.

It is now considered likely that patients with Hashimoto's encephalopathy have other autoantibodies which are more likely to be the pathogenic mediators of disease, such as anti-NMDAR antibodies (in the context of encephalitis), or anti-MOG antibodies (in the context of demyelination). Therefore patients with suspected 'Hashimoto's encephalopathy' may be better categorised under autoimmune encephalitis, either associated with known cell surface antibodies, or seronegative suspected autoimmune encephalitis (as described in this section).

Justification for Evidence Category

Owing to the recent recognition of this condition and its rarity, there are no randomised controlled trials (RCTs) examining the efficacy of intravenous immunoglobulin (IVIg) in anti-NMDA receptor encephalitis. Most publications are of case reports or case series. Cohort studies as described below have been undertaken. In these studies, systemic steroids and IVIg are prescribed in tandem. None have prospectively compared the efficacy of IVIg vs plasmapheresis.

Titulaer et al (2014) described a cohort study of 577 adult and paediatric patients (of whom 501 had follow up of at least four months) with anti-NMDAR encephalitis. 197 (38 percent) had an underlying neoplasm which was resected in 189. First line immunotherapy was defined as the use of steroids, IVIg or plasma exchange alone or in combination. Amongst the 501 patients, 461 (92 percent) were treated with first line immunotherapy (of these, 202 patients received steroids and IVIg) and 134 (27 percent) progressed to second line immunotherapy. Of the patients who received first line treatment, 251 patients achieved treatment response (defined by a reduction in the modified Rankin score to less than four within four weeks). Over the first 24 months, 241 of 251 reached a modified Rankin score of 0-2 (median three months). At 24 months 111 of 115 patients had a good outcome. Publications by the same group have suggested that earlier treatment with both first line and second line therapies is associated with a better outcome.

Armangue et al (2015) reported similar findings in 20 patients aged less than 19 years with anti-NMDAR encephalitis. Nineteen patients received first line immunotherapy at the first episode of encephalitis. All patients received at least a short course of high dose steroids and 14 received IVIg (median two cycles, range 1 to 12 cycles). At median follow up of 17.5 months, 17 (85 percent) had substantial improvement, two had moderate or severe disability and one died. The median time from start of immunotherapy to first sign of improvement was 11.5 days.

International best practice is to use IVIg as first line treatment, concurrently with IV steroids. Escalation to second line therapies should be considered early by the treating physicians after familiarisation with the case literature.

In the systematic review (retrospective case series) by Nosadini et al (2015), three tenets and common themes were reported:

1. Immune therapy is better than no immune therapy
2. If a patient fails to respond to first line therapy, second line therapy improves outcomes. Steroids and IVIg are generally considered first line therapy in anti-NMDAR encephalitis although sometimes plasma exchange is used in addition, or instead of IVIg.
3. No treatment increases the risk of relapse.

Diagnosis Requirements	A diagnosis must be made by a Neurologist.
Qualifying Criteria for Ig Therapy	Confirmed antibody mediated autoimmune encephalitis (AMAE) or limbic encephalitis – cell surface antibody positive • Rapid onset over less than three months of clinical features consistent with a diagnosis of autoimmune antibody mediated encephalitis (AMAE) or limbic encephalitis AND • Testing confirms presence of cell surface neural antibody in CSF (or serum with confirmatory tests e.g. live neurons or tissue immunohistochemistry) AND • Disability as measured by the adapted Modified Rankin Scale (MRS) score to a value of at least two points IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period. Review by a neurologist is required within three months of initiation of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Suspected antibody mediated autoimmune encephalitis (AMAE) – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis

- Sero negative encephalitis or antibody results not yet available

AND

- **Probable AMAE** with a rapid onset over less than three months of at least four symptom groups
  - abnormal (psychiatric) behaviour / cognitive dysfunction,
  - speech dysfunction,
  - seizures,
  - movement disorders;
  - a decreased level of consciousness
  - autonomic dysfunction / central hypoventilation
  - presence of a systemic teratoma

  AND Abnormal EEG or MRI or CSF consistent with encephalitis

  OR

- **Probable limbic encephalitis** with rapid onset over less than three months of working memory deficits (short term memory loss), altered mental status or psychiatric symptoms AND bilateral brain abnormalities on MRI suggestive of encephalitis with CSF pleocytosis and/or EEG abnormalities

  OR

- **Possible autoimmune encephalitis** with rapid onset of less than three months of working memory deficits (short term memory loss), altered mental status or psychiatric symptoms, AND
  - At least one of new focal CNS findings or seizures, AND
  - At least one of abnormal CSF or MRI features suggestive of encephalitis

AND

- Alternative causes have been reasonably excluded

  AND

- Disability as measured by the adapted Modified Rankin Scale (MRS) to a value of at least two points

Note that anti-GAD, thyroid and the classical intracellular antineuronal antibodies in the absence of other listed antibodies should be treated as sero-negative for the purpose of this request.

IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period.

Review by a neurologist is required within three months of treatment to determine whether the patient has responded, and six monthly thereafter.

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

Review Criteria for Assessing the Effectiveness of Ig Use

Confirmed antibody mediated autoimmune encephalitis (AMAE) or limbic encephalitis – cell surface antibody positive

IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period.

Review by a neurologist is required within three months of initiation of treatment to determine whether the patient has responded, and six monthly thereafter.

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

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Clinically significant improvement in the severity of symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) compared to qualifying and no further deterioration in function as assessed by the adapted Modified Rankin Scale score

OR

- No significant improvement in symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) or disability as measured by the adapted Modified Rankin Scale (MRS) and second line treatment with immunosuppressant agents has been commenced

On review of a continuing authorisation period

- Clinical improvement or stability in symptoms (including psychiatric behaviour, cognitive dysfunction, seizures, movement disorders) compared to the previous review

AND

- No further deterioration in disability as measured by the adapted Modified Rankin Scale (MRS) that is less than or equal to the previous review score

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

Suspected antibody mediated autoimmune encephalitis (AMAE) – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis

IVIg should be used for a maximum of three months (induction plus two maintenance cycles) before determining whether the patient has responded. However if a patient has not responded within the first month, the addition of second line treatment should be considered well before the end of that three month period.

Review by a neurologist is required within three months of treatment to determine whether the patient has responded, and six monthly thereafter.

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

- Clinically significant improvement in the severity of symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) compared to qualifying and no further deterioration in function as assessed by the adapted Modified Rankin Scale (MRS)

  OR

- No significant improvement in symptoms or disability as measured by the adapted Modified Rankin Scale (MRS) and second line treatment with immunosuppressant agents has been commenced

AND

- Testing has been undertaken for the presence of antibodies against neural cell surface antigens

On review of a continuing authorisation period

- Clinical improvement or stability in symptoms compared to the previous review

  AND

- No further deterioration in disability as measured by the adapted Modified Rankin Scale (MRS) that is less than or equal to the previous review score

  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	

Confirmed antibody mediated autoimmune encephalitis (AMAE) or limbic encephalitis – cell surface antibody positive

- **Induction Dose (IVIg)** - 2g/kg over 2 - 5 divided days.
- **Maintenance Dose (IVIg)** - 0.4-1g/kg, 4-6 weekly. 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.

IVIg is approved for one induction cycle (2g/kg over 2- 5 days) in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each 0.4-1 g/kg) may be given at which stage the patient must be reviewed to determine whether there has been a clinical response prior to further Ig authorisation.

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.

Suspected antibody mediated autoimmune encephalitis (AMAE) – antibody results not available or sero-negative AMAE or seronegative limbic encephalitis

- **Induction Dose (IVIg)** - 2g/kg over 2 - 5 divided days.
- **Maintenance Dose (IVIg)** - 0.4–1 g/kg, 4 weekly.

Ig therapy is approved for one induction cycle. Two subsequent monthly doses (each 0.4 – 1 g/kg) may be given before initial review.

Ig should be used in conjunction with systemic steroids (unless contraindicated).

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.

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