### 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** |
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| **Condition Name** | **Potassium channel antibody-associated encephalopathy****(**also includes some but not all patients currently eligible under Chapter 7 conditions: Limbic encephalitis — nonparaneoplastic and Limbic encephalitis — paraneoplastic). | **Autoimmune encephalitis mediated by antibodies targeting cell-surface antigens** | | | Chapter 7 has not yet undergone a formal review, however, feedback from the public consultation has requested this condition be developed to re-structure eligible patients covered by several existing conditions in Chapter 7:Potassium channel antibody-associated encephalopathy – all patientsand only those patients with antibodies directed against extra-cellular neural antigens fromLimbic encephalitis — nonparaneoplasticLimbic encephalitis — paraneoplasticas they will respond to Ig therapy.Chapter 7 requires significant review and restructuring including sub acute sensory neuropathy, paraneoplastic cerebellar degeneration, paraneoplastic limbic encephalitis with Ab to intracellular antigens. |
| **Specialty** | Neurology | Neurology | | |  |
| **Chapter** | 7 | 6 | | | A change is recommended as Ig therapy is now recognised internationally as the standard of care in these conditions. |
| **Specific Conditions** |  | Encephalitis associated with antibodies to NMDA Encephalitis associated with antibodies to VGKC Encephalitis associated with antibodies to LGI1 Encephalitis associated with antibodies to ASPR2 Encephalitis associated with antibodies to DPPX Encephalitis associated with antibodies to AMPA Encephalitis associated with antibodies to glycine. | | | The relevant antibodies directed against extracellular neural antigens are described. |
| **Level of Evidence** | Small case studies only (Category 4a). | Large case studies only (Category 4a). | | |  |
| **Description and Diagnostic Criteria** | **Potassium channel antibody-associated encephalopathy** Potassium channel antibody-associated neurologic syndromes include limbic encephalitis/subacute amnesic encephalopathy, Morvan syndrome, peripheral nerve hyperexcitability and autonomic ganglionopathy.  Potassium channel antibody-associated encephalopathy is considered to be an autoimmune, nonparaneoplastic, potentially treatable syndrome, but may respond to a variety of immunomodulatory agents, including IVIg. **Limbic encephalitis — nonparaneoplastic** There appears to be a role for IVIg in nonparaneoplastic limbic encephalitis associated with neuronal antibodies to cell surface antigens. This includes VGKC antibodies, as well as NMDA receptor antibodies and AMPA receptor antibodies.  **Limbic encephalitis — paraneoplastic**  IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention. | Anti-N-methyl-D-aspartate-receptor 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. Patients present with psychiatric symptoms (agitation, paranoia, hallucinations and aggression) which progresses to dyskinesias, seizures, autonomic instability, decreased consciousness, catatonia and central hypoventilation leading to a need for ventilator support in ICU. There are variations on the classical presentation including seizures first, milder forms and cases associated with CNS inflammatory lesions.  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.  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 syndromes described matching particular antibodies but also have some cases described where there is clinical overlap with those described with other antibodies 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. In these cases it may be unclear if the antibody identified is associated with a clinically relevant undesirable response suggesting a need for immunotherapy, or a desirable immune response where immunotherapy may be undesirable.  VGKC-Abs have 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% 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 other antibodies directed against cell surface synaptic antigens (AMPAr, GABAa, GABAb, glycine).  At the time of writing testing is available in Australia for only some of these antibodies. For others samples will need to be sent for testing at international reference laboratories and this is not the role of NBA / ARCBS. 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. | | | Diagnostic criteria, pathological processes and treatment approaches have been updated. |
| **Justification for Evidence Category** |  | Owing to the recent recognition of this condition and its rarity, there are no RCTs examining the efficacy of 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 described a cohort study of 577 adult and paediatric patients (of whom 501 had follow-up of at least 4 months) with anti-NMDAR encephalitis. 197 (38%) 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%) were treated with first line immunotherapy (of these, 202 patients received steroids and IVIg) and 134 (27%) 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 < 4 within 4 weeks). Over the first 24 months, 241 of 251 reached a modified Rankin score of 0-2 (median 3 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 reported similar findings in 20 patients aged less than 19 years with anti-NMDAR encephalitis. 19 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 2 cycles, range 1-12 cycles). At median follow up of 17.5 months, 17 (85%) had substantial improvement, 2 had moderate or severe disability and 1 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. Incrementation to second line therapies should be considered early by the treating physicians after familiarisation with the case literature.  Treatment of other syndromes is less well defined and follows similar lines of immunotherapy plus the use of adjunctive therapies for symptom management. | | | This section has been developed including evidence for Ig treatment. |
| **Diagnosis is required** |  | Yes | By which specialty | Neurologist | Diagnosis is limited to neurologists. |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |  | Anti-GAD or thyroid antibody associated syndromes and the classical intracellular anti-neuronal antibodies are not considered under this condition. | | | Evidence suggests that IVIg is not effective when autoantibodies are directed at intracellular antigens and should only be used in exceptional cases. These are currently listed in Chapter 7 and will be reviewed to be more clearly defined in the next phase of work. |
| **Indications** |  | **First line treatment for autoimmune encephalitis mediated by antibodies targeting neuronal cell surface antigens** | | |  |
| **Qualifying Criteria** | **Potassium channel antibody-associated encephalopathy** Potassium channel antibody-associated neurologic syndromes include limbic encephalitis/subacute amnesic encephalopathy, Morvan syndrome, peripheral nerve hyperexcitability and autonomic ganglionopathy.  Potassium channel antibody-associated encephalopathy is considered to be an autoimmune, nonparaneoplastic, potentially treatable syndrome, but may respond to a variety of immunomodulatory agents, including IVIg. **Limbic encephalitis — nonparaneoplastic** There appears to be a role for IVIg in nonparaneoplastic limbic encephalitis associated with neuronal antibodies to cell surface antigens. This includes VGKC antibodies, as well as NMDA receptor antibodies and AMPA receptor antibodies.    **Limbic encephalitis — paraneoplastic**  IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention. | * Clinical features consistent with antibody mediated autoimmune encephalitis including seizures, cognitive impairment, psychiatric symptoms, dyskinesias, autonomic instability, encephalopathy, catatonia, central hypoventilation   AND   * A baseline assessment of function is measured by the Modified Rankin Score   AND   * Neuronal antibodies to cell surface antigens have been demonstrated, unless tests results are unavailable.   Note anti-GAD or thyroid antibody associated syndromes and the classical intracellular antineuronal antibodies are not considered under this condition.  IVIg is approved for one induction cycle (2g/kg over 5 days) in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each up to 0.4g/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. | | | Given that the symptoms vary with the antibody target, a description of the relevant symptoms for each patient will be captured together with a baseline assessment using the Modified Rankin Score:  0 - No symptoms at all  1 - No significant disability despite symptoms; able to carry out all usual duties and activities  2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance  3 - Moderate disability; requiring some help, but able to walk without assistance  4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily  needs without assistance  5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention  6 Dead  A drop down menu listing the appropriate antibodies will be available. |
| **Review Criteria** |  | 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. Thereafter, six monthly reviews are required.  Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.  **On review of an initial authorisation period**   * Patient demonstrates a clinically significant improvement in the severity of symptoms (including cessation of seizures, improved cognition or conscious state and/or improved psychosis) compared to the severity of symptoms at qualifying   AND   * There has been no further deterioration in function as assessed by the Modified Rankin Score compared to qualifying and Testing confirms the presence of antibodies against neural cell surface antigens (if not already known)   OR   * Patient has failed to demonstrate a clinically significant improvement in symptoms compared to the severity of symptoms at qualifying and as measured by the Modified Rankin Score compared to qualifying value   AND   * Second line treatment with immune-suppressant agents has been commenced   And testing confirms the presence of antibodies against neural cell surface antigens.  **On review of a continuing authorisation period**   * Re-authorisation may only be approved where there is clinical improvement or stability in symptoms   AND   * There has been no further deterioration as measured by a Modified Rankin Score that is greater than or equal to the previous review score   AND   * A trial off Ig therapy is planned or a valid reason provided as to why a trial is not being planned or is contraindicated at this time. | | | Initial therapy has been defined and the timeframe for review set for three months. Review criteria compare severity of symptoms and function (as measured by the Modified Rankin Score) at the initial review compared to qualifying. For patients not responding within three months, the medications used as 2nd line therapy will be recorded.  For patients requiring 2nd line therapy, a response may take longer than three months, however, if response and/or stability in symptoms has not been demonstrated by the next review, Ig therapy is ceased. Most patients will have recovered by that time.  An occasional patient may require treatment for a longer period. A trial off therapy prompt has been included for such cases. |
| **Dose** | **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.  IVIg is approved for one induction cycle in conjunction with systemic steroids (unless contraindicated). Two subsequent monthly doses (each up to 0.4g/kg) may be given before initial review.  **Maintenance** - 0.4–1 g/kg, 4 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.** | | | Dosing is defined, and limited for initial therapy. |

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| **BIBLIOGRAPHY** |
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