### Specialist Working Group for Haematology

#### 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** | Autoimmune haemolytic anaemia | Autoimmune haemolytic anaemia (AIHA) | | |  |
| **Specialty** | Haematology | Haematology | | |  |
| **Chapter** | 6 | 6 | | |  |
| **Specific Conditions** |  | Evan’s Syndrome  AIHA | | | Evan’s Syndrome to be listed as a specific condition for data purposes in both ITP and AIHA given that is recommended to no longer be a separate condition. |
| **Level of Evidence** | Small case studies only; insufficient data ([Category 4a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). | Small case studies only; insufficient data ([Category 4a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). | | |  |
| **Justification for Evidence Category** | An analysis of 73 patients with AIHA in 1993 based on three pilot studies and a literature review showed a 40% response to IVIg given together with corticosteroids. A lower initial haemoglobin concentration and hepatomegaly were positive correlates of response. Several small case series have suggested a benefit for IVIg in AIHA associated with lymphoproliferative diseases, especially CLL. On the basis of these findings, IVIg is not supported as standard therapy for AIHA, only in cases refractory to conventional corticosteroid therapy, as a temporising measure before splenectomy or as maintenance therapy where splenectomy or immunosuppression are not appropriate. | An analysis of 73 patients with AIHA in 1993 based on three pilot studies and a literature review showed a 40% response to IVIg given together with corticosteroids. A lower initial haemoglobin concentration and hepatomegaly were positive correlates of response. Several small case series have suggested a benefit for IVIg in AIHA associated with lymphoproliferative diseases, especially CLL. On the basis of these findings, IVIg is not supported as standard therapy for AIHA, only in cases refractory to conventional corticosteroid therapy, as a temporising measure before splenectomy or as maintenance therapy where splenectomy or immunosuppression are not appropriate.  A 2005 review on the management of Evans syndrome, based on Massachusetts Hospital data and a literature review, showed a transient response in all patients unless IVIg was given every three weeks (Norton and Roberts 2006). The review concluded that the data supported a role for IVIg in first-line therapy. It was not clear whether it was important for steroids to be given at the same time, although this is common practice. A total dose of 2 g/kg in divided doses appeared to be sufficient. The review also stated that there might be a role for IVIg in preference to steroids in the acute setting in very young children.  A recent meta-analysis of 13 small RCTs comparing high dose (2g/kg) to lower dose (1g/kg) IVIg in acute ITP demonstrated equivalent efficacy for all endpoints including platelet responses and control of bleeding (Qin YH et al 2010). | | | A review of the literature has revealed no additional references for IVIg use. The trend as evidence has evolved is for guideline authors to move away from IVIg with advances in other immunosuppressants (rituximab and to some extent MMF).  However, other than occasional case reports, there has been no new evidence for or against AIHA.  As the alternative immunosuppressants are not approved or funded for AIHA, the SWG recommends no change to this section. Script has been added to screen as reminder that corticosteroids are cornerstone of treatment and some response to CD20 antibodies. |
| **Description and Diagnostic Criteria** | AIHA is a rare but serious autoimmune disease in which an individual’s antibodies recognise antigens on their own red blood cells. AIHA presents as an acute or chronic anaemia characterised by the occurrence of biochemical parameters of red cell destruction associated with a positive direct antiglobulin test indicating the presence of antibodies and/or complement on the red cell surface. It may be secondary to a number of underlying disorders or drugs.  **Investigations**  A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum lactate dehydrogenase is raised, and there is a reduction in serum haptoglobin.  **Prognosis**  The prognosis of AIHA is good in most cases although severe refractory AIHA can cause cardio-respiratory problems because of severe anaemia, especially in adults.  **Standard therapy**  Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease. | AIHA is a rare but serious autoimmune disease in which an individual’s antibodies recognise antigens on their own red blood cells. AIHA presents as an acute or chronic anaemia characterised by the occurrence of biochemical parameters of red cell destruction associated with a positive direct antiglobulin test indicating the presence of antibodies and/or complement on the red cell surface. It may be secondary to a number of underlying disorders or drugs.  Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of AIHA and immune thrombocytopenia purpura (ITP) without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders, such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out. The 2005 review by Norton and Roberts provided perspective on diagnosis, clinical features and management.  **Investigations**  A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum lactate dehydrogenase is raised, and there is a reduction in serum haptoglobin.  **Prognosis**  The prognosis of AIHA is good in most cases although severe refractory AIHA can cause cardio-respiratory problems because of severe anaemia, especially in adults.  **Standard therapy**  Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease. | | |  |
| **Diagnosis is required** |  | yes | Which Speciality | Haematologist or Specialist physician or paediatrician | Previously not stated (A) |
| **Diagnosis must be verified** |  | No | Which Specialty |  |  |
| **Exclusion Criteria** | Patients in whom a trial of corticosteroids has not been undertaken. |  | | | While the exclusion criteria describes patients in whom corticosteroid therapy has not bee undertaken, this condition must support Ig treatment of those patients where corticosteroids are contraindicated. |
| **Indication for use** | To reduce haemolysis in patients not responding to corticosteroid therapy. | **To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy**  **Intermittent therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  **Maintenance therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression** | | | Three indications are recommended – these largely match the qualifying criteria in the current version. |
| **Qualifying Criteria** | 1. Symptomatic or severe AIHA (Hb <60 g/L, except patients with co-morbidities) refractory to conventional therapy with corticosteroids;   OR   1. As a temporising measure before splenectomy;   OR   1. As initial and maintenance therapy in AIHA in patients unsuitable for splenectomy or immunosuppression. | **To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy**  Evidence of symptomatic or severe AIHA with current haemoglobin of less than 60g/L (except where significant co-morbidities exist that would influence the tolerance of anaemia)  AND  Haemolysis persists after at least 14 days of conventional corticosteroid therapy unless steroid therapy is contra-indicated or as a temporising measure before splenectomy.  **Intermittent therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  Symptomatic or severe AIHA with current haemoglobin of less than 60g/L (except where significant co-morbidities exist that would influence the tolerance of anaemia)  AND  Haemolysis persists after at least 14 days of conventional corticosteroid therapy unless steroid therapy is contra-indicated  AND  Splenectomy is contraindicated or Immunosuppression is contraindicated  **Maintenance therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  Symptomatic or severe AIHA with current Haemoglobin less than 60g/L (unless significant comorbidities exist) requiring ongoing transfusion support for at least 2 months  AND  Haemolysis persists after at least 14 days of conventional corticosteroid therapy unless steroid therapy is contra-indicated  AND  Splenectomy is contra-indicated or Immunosuppression is contra-indicated. | | | Criteria are largely unchanged from original with steroid therapy being required for at least 14 days.(A)  Steroid contraindication reasons include :   1. Unstable Diabetes 2. Psychosis 3. Mood disorder 4. Significant infection including sepsis 5. Severe osteoporosis 6. History of avascular necrosis   Intermittent therapy is consistent with original criteria.  Contraindication reasons to splenectomy include:   * Extramedullary Haematopoiesis * Surgical contraindication * Age <10   It was noted that there are a very small number of patients on maintenance therapy and it was agreed that this needed to be accommodated provided patients met the criteria as now defined. SWG advised that a 6 month initial review was required with the option to continue treatment ongoing where patients remained transfusion dependant and symptomatic (A) |  |
| **Review Criteria** | * Resolution of haemolytic anaemia (rising haemoglobin concentrations, falling bilirubin and LDH). * Clinical improvement in symptoms and signs. | **Review criteria for assessing the effectiveness of Ig use when one-off treatment is given:**   * Resolution of haemolytic anaemia (rising haemoglobin concentrations, diminished transfusion requirement). * Clinical improvement in symptoms and signs.   **Maintenance therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  **Review Is Required** Yes  **Continuing Treatment is permitted** Yes  **Continuing authorisation request is required** Yes  **Maximum Authorised Treatment Period (Initial)** 6 months  **Maximum Authorised Treatment Period (Continuing Reqs)** 6 months  **Who must undertake review** Haematologist  **If review NOT required maximum length of authorisation** N/A  **Consider cessation** Yes  **Consider Cessation Timeframe** 6 months at initial review and at 12 months.  **Review preamble**  **Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, Splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.**  **On review of the authorisation request:**  Haemolysis is unresolved and patient remains transfusion dependant and symptomatic  AND  Contraindications to splenectomy and immunosuppression remain  AND  A trial off therapy is planned or a valid reason provided as to why a trial is not being planned or is contra-indicated. | | | Given that dosing is mostly one-off, outcome data may be entered but will not be mandatory. SWG did not consider the original outcome measures as defined to be robust. The capture of bilirubin and LDH levels was not endorsed.  For maintenance therapy, review is required 6 monthly when cessation should be considered.  Script added to remind prescribers that steroid therapy is the cornerstone of treatment and reference to CD20 antibodies.  Criteria for ongoing treatment defined to be persistent anaemia and transfusion dependence. |
| **Dose** | Up to 2 g/kg as a single or divided dose.  **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.** | Initial therapy: Recommended dose is 0.8g/Kg as a single dose or divided dose.  [Dose Postscript]  **Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, Splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.**  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.**  **Intermittent therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  **Initial therapy**: 0.8g-2g /kg as a single dose or divided dose.  [Dose Postscript]  **Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, Splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.**  **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.**  **Maintenance therapy for AIHA in patients unsuitable for Splenectomy or immunosuppression**  0.8g-2g /kg as a single dose or divided dose 4 to 6 weekly  [Dose Postscript]  **Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, Splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.** | | | SWG reviewed the minimum dose per Kg and revised the dose to 0.8g/Kg from the previously stated dose of up to 2g/Kg. A maximum dose of 2 g/Kg allowed. |

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| **POTENTIAL OPERATIONAL IMPACT** | | | | |
| No operational impact Is expected due to the transitioning of this condition to the revised Criteria. | | | | |
| **POTENTIAL IMPACT ON DEMAND** | | | |
| **2013-14**  **Patient Numbers**  **Usage** | **126 patients**  **<1%** | No impact is expected on demand given the very low patient numbers. |  |
| **POTENTIAL IMPACT ON COST** | | | |
| **Current cost** |  | **Anticipated reduction in cost, if any**  **Marginal** = borderline or unchanged from current cost  **Minor** = decrease by $500K - $1.99M from current cost  **Major** = decrease $2M+ from current cost | **Marginal** |
| **BIBLIOGRAPHY** | | | | |
| Besa, EC 1988, ‘Rapid transient reversal of anaemia and long-term effects of maintenance intravenous immunoglobulin for autoimmune haemolytic anaemia in patients with lymphoproliferative disorders’, *American Journal of Medicine*, vol. 84, no. 4, pp. 691–8.  Darabi, K, Abdel-Wahab, O & Dzik, WH 2006, ‘Current usage of intravenous immunoglobulin and the rationale behind it: the Massachusetts General Hospital data and review of the literature’, *Transfusion*, vol. 46, no. 5, pp. 741–53.  Flores, G, Cunningham-Rundles, C, Newland, AC, et al 1993, ‘Efficacy of intravenous immunoglobulin in the treatment of autoimmune haemolytic anaemia: results in 73 patients’, *American Journal of Hematology*, vol. 44, no. 4, pp. 237–42.  Majer, RV & Hyde, RD 1988, ‘High-dose intravenous immunoglobulin in the treatment of autoimmune haemolytic anaemia’, *Clinical and Laboratory Haematology*, vol. 10, no. 4, pp. 391–5.  Mathew, P, Chen, G & Wang, W 1997, ‘Evans syndrome: results of a national survey’, *Journal of Pediatric Hematology/Oncology*, vol. 19, no. 5, pp. 433–7.  Norton, A & Roberts, I 2006, ‘Management of Evans syndrome’, *British Journal of Haematology*, vol. 132, no. 2, pp. 125–37.  Sherer, Y, Levy, Y, Fabbrizzi, F, et al 2000, ‘Treatment of hematologic disorders other than immune thrombocytopenic purpura with intravenous immunoglobulin (IVIg) – report of seven cases and review of the literature’, *European Journal of Internal Medicine*, vol. 11, pp. 85–8.  Qin, YH et al 2010, The efficacy of different dose intravenous immunoglobulin in treating acute idiopathic thrombocytopenic purpura: a meta-analysis of 13 randomized controlled trials, *Blood Coagulation and Fibrinolysis* 2010, vol 21, pp713–721. | | | | |
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