### 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, EDITION 2** | **PROPOSED REVISIONS TO THE CRITERIA**  | **SWG RATIONALE FOR PROPOSED CHANGE****(A) Administrative)****(B) Progressive** **(C) Programmed** |
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| **Condition Name** | **Haemophagocytic syndrome** | **Haemophagocytic syndrome** |  |
| **Specialty** | Haematology | Haematology | Haemophagocytic syndrome |
| **Chapter** | 6 | 6 |  |
| **Specific Conditions** |  |  |  |
| **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** | No RCTs have been done, although many, mostly small, case series show evidence of benefit. | No randomised controlled trials (RCTs) have been done, although many, mostly small, case series show evidence of benefit. |  |
| **Description and Diagnostic Criteria** | Haemophagocytic syndrome is characterised by fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow and other tissues with peripheral blood cytopenias. Haemophagocytic syndrome has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman 2000). Mortality is high. | Haemophagocytic syndrome is characterised by fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow and other tissues with peripheral blood cytopenias. Haemophagocytic syndrome has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman 2000). Mortality is high. |  |
| **Diagnosis is required** |  | No | Which Speciality |  |  |
| **Diagnosis must be verified** |  | No | Which Specialty |  |  |
| **Exclusion Criteria** |  | Children with hemophagocytic lymphohistiocytosis (HLH) and hypogammaglobulinaemia - see Secondary hypogammaglobulinaemia unrelated to haematological malignancy.  | This indication is only for the treatment of severe refractory HPS. Ig therapy is recommended practice in current international protocols when children undergoing treatment with alternative medications become hypogammaglobulinaemic. This should be treated under secondary hypogammaglobulinaemia if children are eligible under that condition.  |
| **Indication for use** | Management of severe haemophagocytic syndrome not responding to other treatments. | **Management of severe haemophagocytic syndrome not responding to other treatments~~.~~** | Unchanged |
| **Qualifying Criteria** | Bone marrow diagnosis or other biopsy evidence of haemophagocytosis in the characteristic clinical setting.**Note:** Since other therapies (cytotoxic agents) have major potential side effects, optimal therapy is not yet defined. | * Bone marrow diagnosis or other biopsy evidence of haemophagocytosis.

AND* Clinical features characteristic of haemophagocytic syndrome.

AND* Non-response or ineligibility for other treatments.
 | Qualifying criteria are consistent with current criteria Addition of requirement for non response to other therapies and ineligibility for other treatments.Script deleted as not seen to be helpful and non response to other treatments is a qualifying criteria.  |
| **Review Criteria** | Amelioration of cytopenia(s), hepato/splenomegaly and lymphadenopathy if present.Survival or death. | Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. **Outcome data to be measured**Review criteria for assessing the effectiveness of IVIg use can be demonstrated by: * Survival and improvement in:
	+ cytopoenia(s)
	+ hepatosplenomegaly
	+ lymphadenopathy (if present)
	+ neurologic abnormalities.
 | Outcome data are defined.  |
| **Dose** | 2 g/kg is the most widely published dose.Emmenegger et al (2001) reported that better outcomes were associated with early administration of IVIg in their small case series (10 patients).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.** | **Induction Dose** - 2 g/kg is the most widely published dose.Emmenegger et al (2001) reported that better outcomes were associated with early administration of IVIg in their small case series (10 patients).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. | Dosing is unchanged.  |

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| **BIBLIOGRAPHY** |
| Arlet, JB, Le, TH, Marinho, A, et al 2006, ‘Reactive haemophagocytic syndrome in adult onset Still’s disease: report of six patients and review of the literature’, *Annals of the Rheumatic Diseases*, vol. 65, no. 12, pp. 1596–601.Asci, G, Toz, H, Ozkahya, M, et al 2006, ‘High-dose immunoglobulin therapy in renal transplant recipients with hemophagocytic histiocytic syndrome’, *Journal of Nephrology*, vol. 19, no. 3, pp. 322–6.Chen, RL, Lin, KH, Lin, DT, et al 1995, ‘Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis’, *British Journal of Haematology*, vol. 89, no. 2, pp. 282–90.Emmenegger, U, Frey, U, Reimers, A, et al 2001, ‘Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes’, *American Journal of Haematology*, vol. 68, no. 1, pp. 4–10.Fisman, D, 2000, ‘Hemophagocytic syndromes and infection’, *Emerging Infectious Diseases*. Available from: www.cdc.gov/ncidod/ eid/vol6no6/fisman.htm [cited 7 Dec 2007]Freeman, B, Rathore, MH, Salman, E, et al 1993, ‘Intravenously administered immune globulin for the treatment of infection-associated hemophagocytic syndrome’, *Journal of Pediatrics*, vol. 123, no. 3, pp. 479–81.Ostronoff, M, Ostronoff, F, Coutinho, M, et al 2006, ‘Haemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin’, *Bone Marrow Transplantation*, vol. 37, no. 8, pp. 797–8. |
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**lymphoma (NHL) and other relevant ma**