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
Condition Name	**Haemophagocytic syndrome**	**Haemophagocytic syndrome**	
Specialty	Haematology	Haematology	
Chapter	6	6	
Specific Conditions		Histiolymphocytosis Haemophagocytic syndrome	
Level of Evidence	Small case studies only; insufficient data (Category 4a).	Small case studies only; insufficient data (Category 4a).	
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 a molecular diagnosis consistent with HLH (pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STZ11, SH2D1A, or BIRC4 or five of the following eight criteria (Jordan et al): o Fever > or equal to 38C, o Splenomegaly, o Cytopenias affecting at least two of the three lineages in the peripheral blood (Haemaglobin <90g/L, Platelets <10x10 9/L and/or neutrophils<1x10 6/L; o Hypertrigliceridaemia (fasting>3 mmol/L and/or hypofibrinogenaemia <1.5g/gL, o Haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow, spleen, lymph nodes or liver .	This section has been revised to reflect the internationally recognised diagnostic criteria published by Jordan M.B, Allen C.E, Weitzman S. et al 2011. *Blood* vol. 118 (15), pp 4041-4052. This reference has also been added to the bibiograpy and is used in the qualifying criteria.

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		o Low or absent NK-cell activity, o Ferritin >500ug/L o Elevated sCD25 (alpha chain of sIL-2 receptor) ~~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.	
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.	
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

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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.	• Clinical and laboratory features characteristic of haemophagocytic syndrome and consistent with the diagnostic criteria (*Jordan et al 2011.)* AND • Non-response or ineligibility for other treatments.	Qualifying criteria have been revised to reflect published diagnostic criteria that are currently used in clinical practice internationally. In particular, biopsy evidence is no longer considered diagnostic. 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** • Survival and improvement in clinical and laboratory features: o cytopoenia(s) o hepatosplenomegaly o lymphadenopathy (if present) o neurologic abnormalities.	Outcome data are defined. Minor amendment to reflect the changes above.
Dose	2 g/kg is the most widely published	**Induction Dose** - 2 g/kg is the most widely published dose.	Dosing is unchanged.

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	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.**	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.**	

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.

Jordan M.B, Allen C.E., Weitzman S. et al 2011. *Blood* vol. 118 (15), pp 4041-4052

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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