Haemophagocytic lymphohistiocytosis

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Histiolymphocytosis • Haemophagocytic lymphohistiocytosis • Macrophage activation syndrome
Indication for IVIg Use	• Management of severe haemophagocytic lymphohistiocytosis not responding to other treatments
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Haemophagocytic lymphohistiocytosis (HLH) is an aggressive life threatening disorder of excessive immune activation. Whilst it most frequently affects infants it can also be seen in adults of all ages. Primary HLH refers to the presence of an underlying genetic disorder. Secondary HLH denotes the presence of the HLH phenomenon occurring secondary to another condition. Both primary and secondary forms can be triggered by infections or other immune activating events and the distinction is not essential for the initial diagnosis and management. Macrophage activation syndrome (MAS) is a form of HLH that occurrs primarily in patients with juvenile idiopathic arthritis or other rheumatological conditions. HLH presents as a febrile illness with multi-organ involvement. Common features include fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in the bone marrow and other tissues with peripheral blood cytopenias. Secondary HLH has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman 2000). Mortality is high. Diagnostic criteria for HLH includes either of the following (Jordan et al and McClain and Eckstein): 1. Molecular identification of a HLH associated genetic mutation (PRF1, UN13D, Munc18-2, Rab27a, STZ11, SH2D1A or BIRC4) or 2. Five of the following eight criteria : • Fever > or equal to 38C • Splenomegaly • Cytopenias affecting at least two of the three lineages in the peripheral blood (Haemaglobin <90 g/L, Platelets <10x10^9/L and /or Neutrophils <1x10^9/L) • Hypertriglycerideamia (fasting >3mmol/L and/or hypofibrinogenaemia <1.5g/L) • Haemohphagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow, spleen, lymph nodes or liver • Low or absent NK cell activity • Ferritin >500 ug/L • Elevated sCD25 (alpha chain of sIL 2 receptor)
Justification for Evidence Category	No randomised controlled trials (RCTs) have been done, although many, mostly small, case series show evidence of benefit.

Qualifying Criteria for IVIg Therapy	• Genetic, clinical and/or laboratory evidence supporting a diagnosis of haemophagocytosis (*Jordan et al 2011, McClain and Eckstein 2017).*
Exclusion Criteria	Prevention of infection in children with hypogammaglobulinemia undergoing treatment protocols for haemophagocytic lymphocytosis should be approved under secondary hypogammaglobulinaemia unrelated to haematological malignancy. - see Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Review Criteria for Assessing the Effectiveness of IVIg Use	**Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Survival and improvement in clinical and laboratory features
Dose	• **Dose** - 2 g/kg which may be given over 2 to 5 divisions. 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. Refer to the current product information sheet for further information on dose, administration and contraindication.

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