Acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)

Condition for which Ig has an established therapeutic role.

Specific Conditions	• Acute leukaemia • Chronic lymphocytic leukaemia (CLL) • Memory B cell deficiency secondary to haemopoietic stem cell transplantation (HSCT) • Multiple myeloma (MM) • Non-Hodgkin lymphoma (NHL) • Other Haematological malignancy
Indication for Ig Use	• Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies or post haemopoietic stem cell transplant
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria. A diagnosis of bronchiectasis or suppurative lung disease in patients on Ig therapy must be consistent with the guideline of the Thoracic Society of Australia and New Zealand (Chang AB et al 2014). Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder.
Justification for Evidence Category	One small crossover study of 12 patients with chronic lymphocytic leukaemia (CLL) or non-Hodgkin lymphoma (NHL) reported that the number of serious bacterial infections was significantly decreased ($p = 0.001$) in the months in which patients received IgG every three weeks for one year. Serious bacterial infections showed a trend to be associated with an IgG level less than 6.4 g/L. Three randomised controlled trials (RCTs) and one crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after three to four-weekly administration of IVIg for one year. One placebo-controlled RCT of monthly IVIg given to eighty two multiple myeloma (MM) patients for one year (with 22 withdrawing due to reaction) concluded that IVIg protects against life-threatening infections and significantly reduces risk of recurrent infections. The greatest benefit was seen in individuals who had a poor response to pneumococcal vaccine. A small prospective RCT with 30 MM patients reported a possible decrease in symptoms of chronic bronchitis. A systematic review and meta-analysis (Raanani 2009) of patients undergoing HSCT [60 trials (greater than four thousand patients)] reported an increased risk of veno-occlusive disease with no survival benefit particularly in studies conducted since 2000. The authors concluded that routine prophylaxis with IVIg is not supported, but suggest that its use may be considered in lymphoproliferative disorder patients with hypogammaglobulinaemia and recurrent infections, for reduction of clinically documented infections.
Diagnosis Requirements	A diagnosis must be made by any specialist.

Qualifying Criteria for Ig Therapy	Serum IgG to be measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. • Significant hypogammaglobulinaemia with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections OR • Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age related reference range with at least one life threatening infection in the last 12 months OR • Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age related reference range with at least two serious infections in the last six months requiring more than standard courses of antibiotics (e.g. hospitalisation, intravenous or prolonged antibiotic therapy) Initial review is required within six months by any specialist, with ongoing reviews at least annually to assess clinical benefit. In principle, Ig should be continued or renewed only if there is a demonstrated clinical benefit; therefore documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy. Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.
Exclusion Criteria	Solid organ transplantation - see Solid organ transplantation B cell depletion therapy - see Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency) Thymoma-associated hypogammaglobulinaemia (Goods Syndrome) Transplantation-related immunomodulatory therapy in the absence of hypogammaglobulinaemia Disseminated enterovirus infection without hypogammaglobulinaemia

Review Criteria for Assessing the Effectiveness of Ig Use

Initial review is required within six months by any specialist with ongoing reviews at least annually to assess clinical benefit.

In principle, Ig should be continued or renewed only if there is a demonstrated clinical benefit; therefore documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.

Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Monitoring of serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection

On review of a continuing authorisation period

- Monitoring of serum immunoglobulins (IgG, IgA and IgM) and any history of infection

AND

- There should be regular consideration of a trial period of cessation of IVIg for the purposes of immunological evaluation unless medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppuratives lung disease) or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition. Trial cessation is best commenced in September or October.

  Criterion
  When IgA and IgM are trending upwards and close to normal and the patient is well, a trial off therapy (in September or October) is considered to allow immunological re-evaluation, or is medically contraindicated

Please note: A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the guideline of the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014).

Dose	• **Loading Dose (IVIg)** - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. This dose is also available as subcutaneous immunoglobulin. • **Disseminated Enterovirus Dose (IVIg)** - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. This dose is also available as subcutaneous immunoglobulin. • **Maintenance Dose (IVIg)** - 0.4–0.6g/kg every four weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four week period. Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. • **Supplementary Dose (IVIg)** - One additional dose of 0.4g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4g/L. This dose is also available as subcutaneous immunoglobulin. • **Loading Dose (SCIg)** - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. This dose is also available as intravenous immunoglobulin. • **Disseminated Enterovirus Dose (SCIg)** - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. This dose is also available as intravenous immunoglobulin. • **Maintenance Dose (SCIg)** - 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four week period. This dose is also available as intravenous immunoglobulin. • **Supplementary Dose (SCIg)** - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4g/L. This dose is also available as intravenous immunoglobulin. 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 contraindications.

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