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

Condition for which IVIg 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 IVIg Use
- Prevention of recurrent bacterial infections due to hypogammaglobulinemia 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...
## Diagnosis Requirements

A diagnosis must be made by an Immunologist, Haematologist, Paediatrician, General Medicine Physician or an Oncologist.

## Qualifying Criteria for IVIg 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 a haematologist, general physician or paediatrician and 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
- Disseminated enterovirus infection without hypogammaglobulinaemia
Initial review is required within six months by a haematologist, immunologist, general physician, oncologist or paediatrician and ongoing reviews at least annually to assess clinical benefit.

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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**
- A trial period of cessation of IVIg for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppuratives lung disease or severe hypogammaglobulinemia) persists where no significant improvement has occurred in the underlying condition.

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](https://thoracic.org.au) (Chang AB et al. 2014).
Dose

- **Loading Dose** - 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.

- **Disseminated Enterovirus dose** - One dose of 2 g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection.

- **Maintenance Dose** - 0.4 g/kg every 4 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 4 week period.

Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this condition; a suggested dose is 0.1 g/kg lean body mass every week, modified to achieve a serum IgG level of at least the lower limit of the age specific serum IgG reference range.

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.

Bibliography


Orange, JS, Hosny, EM, Weiler, CR, et al 2006, ‘Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology’, *Journal of Allergy and Clinical Immunology*, vol. 117, no. 4, pp. 5525–53.
Bibliography


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