Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoeitic stem cell transplant (HSCT)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	 Hypogammaglobulinaemia following Solid organ transplantation Hypogammaglobulinaemia following B cell depletion therapy Thymoma-associated hypogammaglobulinaemia (Goods Syndrome) Other Hypogammaglobulinaemia unrelated to haematological malignancies or haemopoietic stem cell transplantation (HSCT)
Indication for IVIg Use	 Replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	An abnormal susceptibility to bacterial infections may arise from acquired hypogammaglobulinaemia that has diverse causes, including haematological malignancies and complications of its treatment (considered in acquired hypogammaglobulinaemia related to haematological malignancy and post haemopoietic stem cell transplantation); protein losing states; malnutrition; thymoma, immunosuppressant therapy; and repeated cycles of B-cell depletion therapy (e.g. rituximab), especially when used with immunosuppressant therapy and in children. In many cases, successful management of the underlying condition will reverse the hypogammaglobulinaemia. However, in some cases, hypogammaglobulinaemia persists and is complicated by recurrent or severe bacterial infections. 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	Approximately 15 percent of patients who have received a solid organ (heart, lung, kidney) transplant experience secondary hypogammaglobulinaemia with severe IgG deficiency (<4g/L) during the first year after transplantation (Florescu DF. Clin Exp Immunol 2014; 178: 54-6). These patients experience a 3·73-fold increased risk of infection when compared with patients who have normal IgG levels and several studies have shown that IVIg therapy reduces the risk of infection in heart and lung transplant patients (Florescu DF. Clin Exp Immunol 2014; 178: 54-6). There is also evidence that subcutaneous immunoglobulin infusions are safe and effective in lung transplant patients (Shankar T et al. Int Immunopharmacol 2013; 15:752–5). Hypogammaglobulinaemia may also be a complication of a thymoma (often known as Good's syndrome). This is usually associated with B cell deficiency. The hypogammaglobulinaemia often increases susceptibility to respiratory tract infections, which are improved by immunoglobulin therapy (Kelesidis T, Yang O. Clinical Immunology 2010; 135: 347–363).
Diagnosis Requirements	A diagnosis must be made by any specialist.

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 and at least one life-threatening infection in the last 12 months

OR

• Serum IgG (excluding paraprotein) greater than 4g/L but less 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)

OR

• Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing

AND

- Underlying cause of hypogammaglobulinaemia cannot be reversed
 OR
- Underlying cause of hypogammaglobulinaemia is reversible but reversal is contraindicated

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

Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

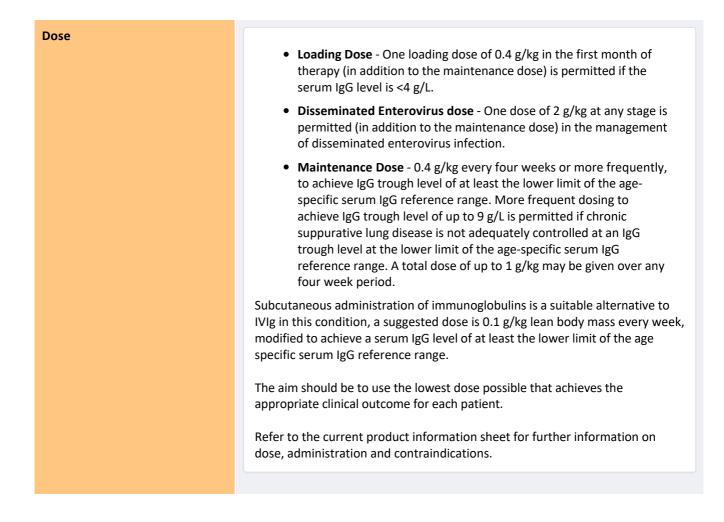
Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig 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.

Secondary hypogammaglobulinaemia related to haematological malignancies or haemopoeitic stem cell transplantation - see <u>Acquired-hypogammaglobulinaemia</u>

Trans - see	ematological malignancy or post HSCT plantation-related immunomodulatory therapy (solid organ transplantation <u>Solid organ transplantation</u> minated enterovirus infection without hypogammaglobulinaemia
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