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

Condition for which Ig 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 Ig 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 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 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 Thoracic Society of Australia and New Zealand (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.
Exclusion Criteria	Secondary hypogammaglobulinaemia related to haematological malignancies or haemopoeitic stem cell transplantation - see Acquired-hypogammaglobulinaemia — haematological malignancy or post HSCT Transplantation-related immunomodulatory therapy (solid organ transplantation) - see Solid organ transplantation Disseminated enterovirus infection without hypogammaglobulinaemia

Review Criteria for Assessing the Effectiveness of Ig Use

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.

On review of the initial authorisation period

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

  AND

- There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe hypogammaglobulinaemia in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October.

  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 unless medically contraindicated.

On review of a continuing authorisation period

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

AND

- There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe hypogammaglobulinaemia in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October.

  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 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 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/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 <4 g/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.

Bibliography

Chang, AB, Bell, SC, Torzillo, PJ, et al 2014, 'Thoracic Sodiety of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand, Clinical Practice Guideline'. Available from: https://www.thoracic.org.au/journal-publishing/command/download_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf

Florescu, DF, 2014, 'Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ

Bibliography

transplantation ’‘Specialist Working Group for Immunology’, *Clinical and Experimental Immunology,* ; no. 178, suppl. 54-6, pp. 54-56.

Kelesidis, T, Yang, O, 2010,’Good’s syndrome remains a mystery after 55 years: A systemic review of the scientific evidence’, *Clinical Immunology,* vol. 135, pp. 347–363.

Orange, JS, Hossny, EM, Weiler, CR, et al 2006, ’Use of intravenous immunoglobulin in human disease: A review of primary 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. S525–53.

Shankar, T, Gribowicz, J, Crespo, M, et al 2013, ‘Subcutaneous IgG replacement therapy is safe and well tolerated in lung transplant recipients’, *Int Immunopharmacology*, vol. 15, issue. 4, pp. 752–755.

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