Primary immunodeficiency diseases (PID) with antibody deficiency

Version: 3.1
Published: 20 October 2018

Condition for which IVIg has an established therapeutic role.

Specific Conditions	• Severe combined immunodeficiency (SCID) • Combined immunodeficiency generally less profound than SCID (e.g. thymoma) • Combined immunodeficiency with associated or syndromal features (e.g. Wiskott Aldrich syndrome; ataxia telangiectasia) • Severe reduction in all Ig isotypes with decreased or absent B-cells (e.g. XLA def) • Severe reduction in at least two Ig isotypes with low/normal B-cells (e.g. CVID) • Severe reduction in serum IgG and IgA with normal/elevated IgM (e.g. CD40L def) • Transient hypogammaglobulinaemia of infancy • Lymphoproliferative syndromes (e.g. XLP1, XLP2, CD27 def) • Possible Common variable immune deficiency (CVID) - below normal serum IgG but normal serum IgA level
Indication for IVIg Use	• Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met • Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level) • Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years) • Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	More than 280 primary immundeficiency diseases (PIDs) have been identified. Many of these cause antibody deficiency. In some cases, antibody deficiency is associated with B-cell deficiency (e.g. X-linked agammaglobulinaemia), while in others, B-cells are present. Antibody deficiency can be the only manifestation of PID, or there can be other defects as well (e.g. T-cell deficiency, autoimmunity). Not all PIDs cause antibody defects and, therefore, immunoglobulin replacement is not always indicated. Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated are: X-linked agamma/hypogammaglobulinaemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, hyper IgM syndrome and severe T-cell immunodeficiency. The revised European Society for Immunodeficiency Diseases (ESID) (2014) diagnostic criteria for common variable immune deficiency (CVID) require the diagnosis to be established after the fourth year of life (but symptoms may be present before) and at least one of the following: • increased susceptibility to infection • autoimmune manifestations • granulomatous disease

	• unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency. AND A marked decrease of immunoglobulin G (IgG) and marked decrease of IgA with or without low IgM levels (measured at least twice; less than the normal reference range for their age). AND At least one of the following: • poor antibody response to vaccines (and/or absent isohemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B-cells (less than 70 percent of age-related normal value). AND Secondary causes of hypogammaglobulinemia have been excluded. The ESID diagnostic criteria for PID have been used as a guide in the development of the qualifying criteria for Ig therapy in Australia. It is acknowledged that a low IgG alone is not a sufficient indication for immunoglobulin replacement. Genetic diagnoses are continually being updated as described in the classification system for the International Union of Immunology Societies (IUIS). It is recognised that genetic diagnoses are not always possible.
Justification for Evidence Category	The Biotext (2004) review reported level 2a evidence for the use of intravenous immunoglobulin (IVIg) in the treatment of common variable immunodeficiency and primary hypogammaglobulinaemia.
Diagnosis Requirements	A diagnosis must be made by an Immunologist.

Qualifying Criteria for IVIg Therapy

Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met

Note: If less than four years the request must be under the indication **Transient hypogammaglobulinaemia of infancy (children aged less than four years)**

- The patient is older than four years of age

AND

Blood samples for IgG and IgA testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection

- Evidence of a marked decrease of IgG and a marked decrease of IgA with or without low IgM levels and causes of secondary hypogammaglobulinaemia have been excluded

AND

- Documented failure of serum antibody response after vaccination with conjugated or unconjugated pneumococcal vaccine or following protein vaccine challenge

  OR

- The patient's serum IgG is less than 2 g/L and a delay to providing Ig replacement (e.g. following an invasive bacterial infection) would present significant risk

  OR

- The patient has absent haemagglutinins (if not blood group AB)

  OR

- The patient has low switched memory B-cells (less than 70 percent of age-related normal value)

AND

- The patient has demonstrated an increased susceptibility to infection

  OR

- The patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation or an affected family member with antibody deficiency

Initial review by an immunologist is required at six months and annually thereafter. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

The review criteria for primary immunodeficiency diseases are to ensure adequate replacement of antibody deficiency and to demonstrate clinical benefit from treatment.

Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)

A low IgG (normal IgA with or without a low IgM) alone is not a sufficient indication for immunoglobulin replacement therapy. Many patients will be well despite the finding of a serum IgG below the normal range for age.

- The patient is older than four years of age

AND

Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection

- Evidence of a marked decrease of IgG with normal IgA (with or without low IgM) levels and causes of secondary hypogammaglobulinaemia have been excluded

AND

- Documented failure of serum antibody response after vaccination with conjugated or unconjugated pneumococcal vaccine or following protein vaccine challenge

  OR

- The patient's serum IgG less than 2 g/L and a delay to providing Ig replacement (e.g. following an invasive bacterial infection) would present significant risk

  OR

- The patient has absent haemagglutinins (if not blood group AB)

  OR

- The patient has low switched memory B-cells (less than 70 percent of age-related normal value)

AND

- The patient has demonstrated an increased susceptibility to infection

  OR

- The patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation or an affected family member with antibody deficiency

Initial review is required by an Immunologist at six months and ongoing reviews 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 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.

This should particularly be considered in patients who do not have active bronchiectasis and/or suppurative lung disease. An immunoglobulin washout period of four to six months is necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of cessation of immunoglobulin therapy.

***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 and the Australian Lung Foundation (Chang et al 2014).**

Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)

The majority of young children with transient hypogammaglobulinaemia do not require immunoglobulin (Ig) therapy. However, if the patient has had recurrent suppurative infections that threaten organ function, review by an immunologist is recommended for consideration of Ig therapy. Some patients may require treatment during the winter months only and others will benefit from more prolonged treatment.

Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection.

- Younger than four years of age at diagnosis

  AND

- Evidence of a marked decrease of IgG and causes of secondary hypogammaglobulinemia have been excluded

AND

- The patient has demonstrated an increased susceptibility to infection

Initial review is required by an Immunologist, at six months, and ongoing reviews 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 24 months of treatment. If serum IgM and IgA levels are trending upwards and close to 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 should 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.

When the child is four years old, a decision must be made regarding a trial off treatment or qualification may be appropriate under a different indication such as possible or confirmed CVID.

	Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.) Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection. • Confirmed or suspected diagnosis of primary immunodeficiency AND • Evidence of hypogammaglobulinaemia Initial review by an Immunologist is required at six months, with reviews annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. Where a diagnosis has initially been suspected, confirmation will be required for access to continuing Ig therapy.
Exclusion Criteria	Acquired hypogammaglobulinaemia secondary to haematological malignancy or post HSCT - see Acquired-hypogammaglobulinaemia — haematological malignancy or post HSCT Specific antibody deficiency - see Specific antibody deficiency (SAD) IgG subclass deficiency - see Specific antibody deficiency (SAD) Secondary hypogammaglobulinaemia unrelated to haematological malignancy or stem cell transplantation - see Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Review Criteria for Assessing the Effectiveness of IVIg Use	Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met Initial review by an immunologist is required at six months and annually thereafter. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. The review criteria for primary immunodeficiency diseases are to ensure adequate replacement of antibody deficiency and to demonstrate clinical benefit from treatment. **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 AND • A diagnosis of CVID has been made **On review of a continuing authorisation period** • Monitoring of serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection

Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)

Initial review is required by an Immunologist at six months and ongoing reviews 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 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.

This should particularly be considered in patients who do not have active bronchiectasis and/or suppurative lung disease. An immunoglobulin washout period of four to six months is necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of cessation of 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

AND

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

On review of a continuing authorisation period

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

AND

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

Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

***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 et al 2014).**

Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)

Initial review is required by an Immunologist, at six months, and ongoing reviews 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 24 months of treatment. If serum IgM and IgA levels are trending upwards and close to 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 should 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.

When the child is four years old, a decision must be made regarding a trial off treatment or qualification may be appropriate under a different indication such as possible or confirmed CVID.

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

AND

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

On review of a continuing authorisation period

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

AND

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

Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

***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 et al 2014).**

Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)

Initial review by an Immunologist is required at six months, with reviews annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

The review criteria for primary immunodeficiency diseases are to ensure adequate replacement of antibody deficiency and to demonstrate clinical benefit from treatment.

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

  AND

- A diagnosis of primary immunodeficiency has been confirmed

On review of a continuing authorisation period

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

  AND

- A diagnosis of primary immunodeficiency has been confirmed

Dose

Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met

- **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 2g/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 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 9g/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 1g/kg may be given over any four week period.

Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1 g/kg lean body mass every week, modified to achieve an IgG trough 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.

Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)

- **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.
- **Dissemination 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 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 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.

Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)

- **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.
- **Maintenance Dose** - .4 g/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. A suggested dose is 0.1 g/kg lean body mass every week, modified to achieve an IgG trough 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.

Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)

- **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 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. A suggested dose is 0.1 g/kg lean body mass every week, modified to achieve an IgG trough 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

Biotext 2004, 'Summary data on conditions and papers', in *A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks*, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 218. Available from: https://www.blood.gov.au/system/files/A-systematic-literature-review-and-report-on-the-efficacy-of-IVIg-therapy-and-its-risks.pdf

Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', *Annals of Allergy, Asthma and Immunology*, vol. 94, no. 5, suppl. 1, pp. S1–63.

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.

Cooper, MD & Schroeder, Jr HW 2005, 'Primary immune deficiency diseases', in DL Kasper, E Braunwald, AS Fauci, et al (eds), *Harrison's Textbook of Medicine*, 16th edn, McGraw-Hill, New York, pp. 1939–47.

Orange, JS, Hossny, 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. S525–53.

Al-Herz, W, Bousfina, A, Casanova, J-L, et al 2014. 'Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.' *Frontiers in Immunology*, Vol 5, article 162, pp1-33. doi: 10.3389/fimmu.2014.00162. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2014.00162/full