

# Specific antibody deficiency

Condition for which Ig has an emerging therapeutic role.

Specific Conditions	<ul style="list-style-type: none"><li>Specific antibody deficiency</li><li>Existing patient - authorisation for IgG subclass deficiency</li></ul>
Indication for Ig Use	<ul style="list-style-type: none"><li>Prevention of recurrent/persistent infections in individuals with a demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels</li><li>Prevention of infection in individuals with proven specific antibody deficiency who have had a life-threatening infection or a series of serious infections following trial-off Ig therapy</li><li>Prevention of infection in patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency provided that a diagnosis of specific antibody deficiency is confirmed following cessation of immunoglobulin therapy</li></ul>
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	<p>The term ‘specific antibody deficiency’ describes failure to produce a normal immunoglobulin G (IgG) antibody response following antigen challenge (post vaccination) in an individual with a normal serum total IgG level. It is most often used in the context of impaired IgG antibody responses against polysaccharide antigens, particularly pneumococcal polysaccharides (Boyle et al 2006).</p> <p>The definition of a low IgG antibody response following vaccination with pneumococcal polysaccharides is still in development (Boyle et al 2006, Hare et al 2009, Borgers et al 2012). For approval of Ig therapy, the patient should exhibit an inadequate serum IgG or IgG2 antibody response to pooled pneumococcal polysaccharides (PcPs), or serotype- specific PcPs, four weeks after a single vaccination with unconjugated pneumococcal polysaccharides. Rarely, patients with an increased susceptibility to respiratory tract infections exhibit impaired antibody responses to protein antigens, such as tetanus toxoid. A definition of an abnormal antibody response is not clearly established, but failure to produce a ‘protective’ serum level of IgG antibodies against tetanus toxoid following at least two vaccinations should be considered abnormal. Assessment of IgG antibody responses following vaccination with Haemophilus influenzae type B (Hib) may also be undertaken.</p> <p>Immunoglobulin therapy may be indicated for patients with chronic suppurative ear, sinus or lung disease and/or bronchiectasis who present with evidence of abnormally recurrent or persistent bacterial infections, with a documented requirement for antibiotic therapy, associated with a low IgG antibody response following vaccination with pneumococcal polysaccharides or tetanus toxoid (see above).</p> <p>Further research investigating clinical and laboratory features of this group of disorders is required.</p>
Justification for Evidence Category	<p>The effectiveness of IgG therapy in preventing infections in patients with specific antibody deficiency (SAD) has been assessed in retrospective studies (Orange et al, 2006). Despite a lack of definitive data, a number of published expert guidelines including the Joint Council of Allergy, Asthma and Immunology (JCAAI) on behalf of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma &amp; Immunology (Bonilla et al 2015), and the United Kingdoms’ Clinical Guidelines for Immunoglobulin Use of the (2011), and expert opinion (Perez et al, 2017) have recommended IgG therapy in patients with SAD. The AAAAI, ACAAI, and JCAAI practice parameter recommends that patients who have stabilised after a period of IgG treatment, and are deemed at low risk for relapse, should discontinue IgG treatment for a period of four to six months to reevaluate therapy (Bonilla et al, 2015).</p>
Diagnosis Requirements	<p>A diagnosis must be made by an Immunologist.</p>

Prevention of recurrent/persistent infections in individuals with a demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels

This indication should be used for new patients and those that have never trialled off Ig therapy. For responding patients who have relapsed after weaning from Ig therapy please use the indications:

**Prevention of infection in individuals with proven specific antibody deficiency who have had a life-threatening infection or a series of serious infections following trial-off Ig therapy or Prevention of infection in patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency provided that a diagnosis of specific antibody deficiency is confirmed following cessation of immunoglobulin therapy.**

- Recurrent and/or persistent and significant infections despite oral antibiotic prophylaxis therapy

AND

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

Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.

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

Cessation of immunoglobulin therapy should be considered at least after each 12 months of Ig therapy, extended as required to enable cessation of therapy in September or October.

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.

Following a trial off Ig therapy, patients may qualify for further immunoglobulin therapy:

- under other immunodeficiency criteria (e.g. primary antibody deficiency disorder), depending on the results of subsequent immune evaluation; or
- rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation.

In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with unconjugated pneumococcal polysaccharide vaccine is not recommended because of the potential for immune hypo-responsiveness induced by repeated vaccination (O'Brien et al 2007).

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 [Thoracic Society of Australia and New Zealand](#) (Chang AB et al. 2014)**

Prevention of infection in individuals with proven specific antibody deficiency who have had a life-threatening infection or a series of serious infections following trial-off Ig therapy

This indication should be used for responding proven specific antibody deficiency (SAD) patients who have begun a trial off immunoglobulin therapy. For new patients and those that have never trialled off from Ig therapy, please use the indication: **Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels.**

- Patient with proven specific antibody deficiency undertaking a trial off Ig therapy

AND

- At least one life-threatening bacterial infection in the previous 12 months

OR

- 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)

Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.

Regular review by an immunologist or respiratory physician is required, in the first six months and then at least annually. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Cessation of immunoglobulin therapy should be considered, at least after each 12 months of Ig therapy, extended as required to enable cessation of therapy in September or October.

This should particularly be considered in patients who do not have suppurative lung disease or bronchiectasis. 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.

Following a trial off Ig therapy, patients may qualify for further immunoglobulin therapy:

- under other immunodeficiency criteria (e.g. primary antibody deficiency disorder), depending on the results of subsequent immune evaluation; or
- rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation.

In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with unconjugated pneumococcal polysaccharide vaccine is not recommended because of the potential for immune hypo responsiveness induced by repeated vaccination (O'Brien et al 2007).

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 [Thoracic Society of Australia and New Zealand](#) (Chang AB et al. 2014)**

	<p>Prevention of infection in patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency provided that a diagnosis of specific antibody deficiency is confirmed following cessation of immunoglobulin therapy</p> <p>This indication should be used for <b>patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency who are eligible for continued therapy</b>. For new patients and those that have previously trialled off from Ig therapy, please use the indication <b>Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels</b>.</p> <ul style="list-style-type: none"> <li>Existing patient with a diagnosis of IgG subclass deficiency on IgG therapy funded under the National Blood Arrangements in Australia</li> </ul> <p>Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.</p> <p>Regular review by an immunologist or respiratory physician is required, at least annually. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.</p> <p>Cessation of immunoglobulin therapy should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September or October.</p> <p>This should particularly be considered in patients who do not have active suppurative lung disease or bronchiectasis. An immunoglobulin washout period of four to six months is necessary to enable an accurate assessment and immunological re-evaluation. Prophylactic antibiotics may be considered to cover the period of cessation of immunoglobulin therapy.</p> <p>In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit and ceasing therapy will compromise patient safety.</p> <p>Antibiotic therapy may be indicated in addition to immunoglobulin therapy.</p>
<b>Exclusion Criteria</b>	<p>Isolated IgG subclass deficiency in the absence of evidence of specific antibody deficiency</p> <p>Low serum total IgG. This should be considered under primary or secondary hypogammaglobulinaemia</p>

Prevention of recurrent/persistent infections in individuals with a demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels

Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.

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

Cessation of immunoglobulin therapy should be considered at least after each 12 months of Ig therapy, extended as required to enable cessation of therapy in September or October.

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.

Following a trial off Ig therapy, patients may qualify for further immunoglobulin therapy:

- under other immunodeficiency criteria (e.g. primary antibody deficiency disorder), depending on the results of subsequent immune evaluation; or
- rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation.

In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with unconjugated pneumococcal polysaccharide vaccine is not recommended because of the potential for immune hypo-responsiveness induced by repeated vaccination (O'Brien et al 2007).

Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

**Evidence of clinical effectiveness of Ig therapy, and criteria for continued use may include:**

**On review of the initial authorisation period**

- The patient has demonstrated clinical benefit during the review period
- AND
- The patient's infection history during the review period has been monitored

AND

- A trial period of cessation of immunoglobulin for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, on immunosuppressant medication or clinically active bronchiectasis and/or suppurative lung disease\*)

**On review of a continuing authorisation period**

- The patient has demonstrated clinical benefit during the review period
- AND
- The patient's infection history during the review period has been monitored

AND

- A trial period of cessation of Ig therapy for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, on immunosuppressant medication or clinically active bronchiectasis and/or suppurative lung disease\*)

**\*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)**

Prevention of infection in individuals with proven specific antibody deficiency who have had a life-threatening infection or a series of serious infections following trial-off Ig therapy

Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.

Regular review by an immunologist or respiratory physician is required at least annually. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Cessation of immunoglobulin therapy should be considered, at least after each 12 months of Ig therapy, extended as required to enable cessation of therapy in September or October.

This should particularly be considered in patients who do not have suppurative lung disease or bronchiectasis. 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.

Following a trial off Ig therapy, patients may qualify for further immunoglobulin therapy:

- under other immunodeficiency criteria (e.g. primary antibody deficiency disorder), depending on the results of subsequent immune evaluation; or
- rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation.

In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with unconjugated pneumococcal polysaccharide vaccine is not recommended because of the potential for immune hypo responsiveness induced by repeated vaccination (O'Brien et al 2007).

Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

**Evidence of clinical effectiveness of Ig therapy, and criteria for continued use may include:**

**On review of the initial authorisation period**

- The patient has demonstrated clinical benefit during the review period
- AND
- The patient's infection history during the review period has been monitored

AND

- A trial period of cessation of immunoglobulin for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, on immunosuppressant medication or clinically active bronchiectasis and/or suppurative lung disease\*)

**On review of a continuing authorisation period**

- The patient has demonstrated clinical benefit during the review period
- AND
- The patient's infection history during the review period has been monitored

AND

- A trial period of cessation of Ig therapy for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, on immunosuppressant medication or clinically active bronchiectasis and/or suppurative lung disease\*)

**\*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).**

Prevention of infection in patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency provided that a diagnosis of specific antibody deficiency is confirmed following cessation of immunoglobulin therapy

Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children.

Regular review by an immunologist or respiratory physician is required, at least annually. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Cessation of immunoglobulin therapy should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September or October.

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

In principle, immunoglobulin therapy should only be continued or renewed if there is a demonstrated clinical benefit and ceasing therapy will compromise patient safety.

Antibiotic therapy may be indicated in addition to immunoglobulin therapy.

**Evidence of clinical effectiveness of Ig therapy, and criteria for continued use may include:**

**On review of the initial authorisation period**

- Existing patient on IgG therapy funded under the National Blood Arrangements in Australia
- AND
- The patient has demonstrated clinical benefit during the authorisation period

AND

- A trial period of cessation of Ig therapy for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as a patient with neutropenia, on immunosuppressant medication or with clinically active bronchiectasis and/or suppurative lung disease\*)

**On review of a continuing authorisation period**

- The patient has demonstrated clinical benefit during the authorisation period
- AND
- Clinically active bronchiectasis and/or suppurative lung persists (see note\*)

AND

- A trial period of cessation of Ig therapy for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, on immunosuppressant medication or clinically active bronchiectasis and/or suppurative lung disease\*)

**\*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)**

Dose

Prevention of recurrent/persistent infections in individuals with a demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge, despite normal total serum IgG levels

- **Maintenance Dose (IVIg)** - 0.4g/kg is permitted every 4 weeks.  
Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg.
- **Maintenance Dose (SCIg)** - 0.1g/kg is permitted every 1 week.  
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.

Prevention of infection in individuals with proven specific antibody deficiency who have had a life-threatening infection or a series of serious infections following trial-off Ig therapy

- **Maintenance Dose (IVIg)** - 0.4g/kg is permitted every 4 weeks.  
Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg.
- **Maintenance Dose (SCIg)** - 0.1g/kg is permitted every 1 week.  
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.

Prevention of infection in patients currently receiving immunoglobulin therapy for a diagnosis of IgG subclass deficiency provided that a diagnosis of specific antibody deficiency is confirmed following cessation of immunoglobulin therapy

- **Maintenance Dose (IVIg)** - 0.4g/kg is permitted every 4 weeks.  
Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg.
- **Maintenance Dose (SCIg)** - 0.1g/kg is permitted every 1 week.  
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

Bheng, YK, Decker, PA, O’Byrne, MM, et al 2006, ‘Clinical and Laboratory characteristics of 75 patients with specific Polysaccharide antibody deficiency syndrome’, *Annals of Allergy, Asthma and Immunology*, vol. 97, no. 3, pp. 306–11.

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.

Bonilla, FA, Bernstein, L, Khan, DA, et al 2015, ‘Practice parameter for the diagnosis and management of primary immunodeficiency’, *Journal of Allergy and Clinical Immunology*, vol. 136, no. 5, pp. 1186-205. doi:10.1016/j.jaci.2015.04.049

Borgers, H, Meyts, I, De Boeck, K et al 2012, ‘Fold-increase in antibody titer upon vaccination with pneumococcal unconjugated polysaccharide vaccine’, *Clinical Immunology*, vol. 145, pp. 136–8.

Boyle, RJ, Le, C, Balloch, A, et al 2006, ‘The clinical syndrome of specific antibody deficiency in children’, *Clinical and Experimental Immunology*, vol. 146, pp. 486–92.

Chang, AB, Bell, SC, Byrnes, CA et al 2010, ‘Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand’, *Medical Journal of Australia*, vol. 193, pp. 356–65.

## Bibliography

Chang AB, Bell SC, Torzillo PJ, et al 2014, Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline. [https://www.thoracic.org.au/journal-publishing/command/download\\_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf](https://www.thoracic.org.au/journal-publishing/command/download_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf) [cited June 2018]

*Guidelines for Immunoglobulin Use*. 2nd ed. UK: Department of Health (2011). Available from: [http://www.ivig.nhs.uk/documents/dh\\_129666.pdf](http://www.ivig.nhs.uk/documents/dh_129666.pdf) 53. Hare, ND, Smith, BJ & Ballas, ZK 2009, 'Antibody response to pneumococcal vaccination as a function of pre-immunization titer', *Journal of Allergy and Clinical Immunology*, vol. 123, pp. 195–200.

O'Brien, KL, Hochman, M & Goldblatt, D 2007, 'Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue?' *Lancet Infectious Diseases*, vol. 7, no. 9, pp. 597–606.

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

Orange, JS, Ballow, M, Stiehm, ER, Ballas, ZK, Chinen, J, De La, Morena, M, et al 2012, 'Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology.', *Journal of Allergy Clinical Immunology*, vol. 130, suppl. 3, pp. 1-24.

Perez, E, Bonilla, FA, Orange, JS & Ballow, M 2017, 'Specific antibody deficiency: Controversies in Diagnosis and Management', *Frontiers in Immunology*, vol. 8, no. 586. doi: 10.3389/fimmu.2017.00586

*Generated on: 10 December 2024*