Specialist Working Group for Immunology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)**	**Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoeitic stem cell transplant (HSCT)**	The condition name has been revised to more clearly align with the other Secondary hypogammaglobulinaemia condition but clearly differentiate what is included. (A)
Specialty	Immunology	Immunology, Solid Organ Transplantation	
Chapter	6	6	
Specific Conditions		Solid organ transplantation B cell depletion therapy Thymoma-associated hypogammaglobulinaemia (Goods Syndrome) Other	
Level of Evidence	No included studies (Category 4b).	Small case studies only, insufficient data (Category 4a).	Level of evidence upgraded in line with literature review (A)
Description and Diagnostic Criteria	Recurrent and/or severe bacterial infections may arise from hypogammaglobulinaemia of diverse causes. Hypogammaglobulinaemia may arise from protein losing states, malnutrition and medical immunosuppression. In most cases, successful management of the underlying condition will reverse the	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 Chapter 5); protein losing states; malnutrition; thymoma, immunosuppressant therapy; and repeated cycles of B-cell depletion therapy (eg. Rituximab), especially when used with immunosuppressant therapy and in children	Section revised. Following public consultation, an additional script was added to highlight the potential for disseminated enterovirus infection as a risk in patients with secondary hypogammaglobulinemia. (A)

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	immunodeficiency, restoring immunocompetence. In some cases, recurrent or severe infection may arise from secondary immunodeficiency where the underlying cause cannot be reversed, or where there are unwanted effects of removing or reducing immunosuppressive therapy. New immunosuppressive regimens such as monoclonal B-cell depletion with Rituximab or similar agents do not generally induce hypogammaglobulinaemia at standard doses. However, repeated cycles of B-cell depletion in combination with other agents used to treat life-threatening immune-mediated diseases may increase rates of infection related to hypogammaglobulinaemia.	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 occassionally 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% 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*	Section has been introduced from literature review. (A)

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		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 is required		No / Which Speciality	
Diagnosis must be verified		No / Which Specialty	
Exclusion Criteria	Reversible underlying cause of hypogammaglobulinaemia. The following conditions should not be	Secondary hypogammaglobulinaemia related to haematological malignancies or haemopoeitic stem cell transplantation - see relevant condition; Transplantation-related immunomodulatory therapy (kidney and other solid organ transplantation) - see relevant condition.	Reversible causes of hypogammaglobulinaemia are eligible for treatment of this condition so this has been deleted. Exclusions have been reworded to more clearly indicate where a different condition

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	approved under this indication: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation (see page 48); 2. HIV in children (see page 185); or 3. Transplantation related immunomodulation (solid organ transplantation; see page 208).	Disseminated enterovirus infection without hypogammaglobulinaemia.	should be selected (which will be directly referred with in the BloodSTAR system). A new exclusion was added post the public consultation discussion regarding disseminated enterovirus infection.
Indication for use	Replacement therapy for life-threatening infection due to hypogammaglobulinaemia related to other diseases or medical therapy. **Note:** The following secondary causes of hypogammaglobulinaemia are considered elsewhere: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell	**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.** **Chronic suppurative lung disease associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy.**	Indication reworded to more clearly distinguish eligible patients from other conditions. A second indication has been created to support increased dosing allowable for patients with chronic suppurative lung diseases. (A)

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	transplantation (see page 48) 2. HIV in children (see page 185) 3. Solid organ transplantation (see page 208)		
Qualifying Criteria	Hypogammaglobulinaemia secondary to underlying disease or medical therapy (including haemopoietic stem cell transplantation [HCST]) with all the following: 1. Serum IgG less than the lower limit of the reference range on two separate occasions; AND 2. Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; AND 3. At least one of the following: 1. One invasive or life-	**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.** [Group1] • Serum IgG less than the lower limit of the reference range 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 IgA and IgM levels should be provided to allow assessment of immune recovery at review. AND • Underlying cause of hypogammaglobulinaemia cannot be reversed or underlying cause of hypogammaglobulinaemia is reversible but reversal is contraindicated AND [Group 2] • Patient has had one life-threatening bacterial infection in the previous 12 months	HSCT is included under the other secondary hypogammaglobulinaemia given that all HSCT patients are managed by haematologists. Qualifying criteria have been defined including the assessment of baseline serum IgM and IgA levels because if they are normalising, this may suggest recovery of the immune system. Clarification has been provided regarding the approach to blood sampling to confirm low serum IgG on two separate occasions. It is noted that IgG levels can drop during acute infections and therefore, at least one sample should be taken once the patient has recovered. An evidence item has been added to capture the presence of paraproteins which may interfere with serum immunoglobulin result interpretation. Consistency with the other relevant condition has been applied. (A)

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	threatening bacterial infection (e.g. pneumonia, meningitis, sepsis) in the previous year; or 2. Clinically active bronchiectasis confirmed by radiology.	OR • At least two serious infections in the last six months requiring more than standard courses of antibiotics (eg. Hospitalisation, intravenous or prolonged antibiotic therapy). OR • Evidence of impaired antibody production in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing. OR • Patient has significant hypogammaglobulinaemia with serum IgG level <4g/L and information regarding the frequency and severity of infections requiring treatment in last 6 months must be provided. Antibiotic therapy may be indicated in addition to Immunoglobulin therapy. **Chronic suppurative lung disease associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy.** • Serum IgG less than the lower limit of the reference range measured on two separate occasions (at least one hour apart and at least	Evidence supports the treatment of patients with IgG <4g/L without a history of infection (see other secondary hypogammaglobulinemia related to haematological malignancy) and consistency has been applied across both conditions. (A)

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		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. AND • Underlying cause of hypogammaglobulinaemia cannot be reversed or underlying cause of hypogammaglobulinaemia is reversible but reversal is contraindicated AND • Patient has clinically active bronchiectasis* or suppurative lung disease confirmed by radiology with more than two acute episodes in the last 12 months. ***Please note: A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with position statement of the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation (Chang AB et al. Med J Australia 2010; 193:356-65).** Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	
Review Criteria	Six-monthly review to assess clinical benefit.	**Severe bacterial infections or disseminated enterovirus infection associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or**	Review criteria have been defined and serum Ig A and M can be used to assess the recovery of immunocompetence and potential suitability for a trial off Ig G

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	Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. Written confirmation from the treating physician that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.	**immunosuppressant therapy.** Initial review is required at six months and ongoing reviews at least annually by the Treating Medical Specialist to assess clinical benefit. Documentation of clinical effectiveness if 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 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 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 re-commencement of therapy. **On review of the authorisation period** • An assessment of the clinical benefit during the review period will be made and trough or serum immunoglobulin levels (IgG, IgA and IgM) and a history of infection must be reviewed. AND • A trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds (such as	therapy. (A) SWG advises that if a patient should trial off and require Ig therapy again - the patient would need to requalify.(A) Statements regarding IgA and IgM levels have been revised to improve the clinical guidance being provided regarding timing of trialling off Ig therapy. It is recognised that the decision to trial off Ig therapy is a clinical one, rather than being mandated by Ig levels. A diagnosis of chronic suppurative lung disease or active bronchiectasis must comply with the requirements of the position statement of the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation. Script acknowledging that antibiotic therapy may be required in addition to Ig treatment. (A)

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		patient has neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease* or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition). OR • A trial cessation of therapy will be undertaken next September or October to undertake an immunological evaluation. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit. Antibiotic therapy may be indicated in addition to Immunoglobulin therapy. **Chronic suppurative lung disease associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy.** ***Please note: A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with position statement of the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation (Chang AB et al. Med J Australia 2010; 193:356-65).** Initial review is required at six months with subsequent reviews at least annually by the Treating	

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		Medical Specialist to assess the 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 close to normal 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 re-commencement of therapy. **On review of an authorisation period** • An assessment of the clinical benefit during the review period will be made and trough or serum immunoglobulins (IgG, IgA and IgM) and a history of infection must be reviewed. AND • A trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medications, active bronchiectasis and/or suppurative lung disease* or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition).	

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		OR • A trial cessation of therapy will be undertaken next September or October to undertake an immunological evaluation. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit. Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modified to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. **Chronic suppurative lung disease:** 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.	**Loading Dose** - One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is < 4g/L. **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. A total dose of up to 1 g/Kg may be given over any 4 week period which might be by divided doses more frequently than monthly. **Chronic suppurative lung disease.** 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. Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this condition.	Dosing is unchanged but upper dose limits have been defined by stating a total monthly dose. (A) The SWG advises that improved clinical benefit will come from dosing slightly more frequently (within the total dose allocation that was not previously defined) rather than just increasing the monthly dose. This will reduce the 'highs' and 'lows' of serum IgG. (A)

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	Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	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.**	

BIBLIOGRAPHY

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.

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