

Specialist Working Group for Haematology

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, EDITION 2	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative (B) Progressive (C) Programmed
Condition Name	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)	Secondary hypogammaglobulinaemia related to haematological malignancies and post haemopoietic stem cell transplantation	The name of the condition was changed to align with Secondary hypogammaglobulinaemia unrelated to haematological malignancy. These are similar conditions but have been kept separate in order to more easily track patients within specialties. (A)
Specialty	Haematology	Immunology & Haematology	Review has been undertaken by both Haematology and Immunology SWGs to assure consistency for the two conditions. (A)
Chapter	5	5	
Specific Conditions		Chronic lymphocytic leukaemia (CLL); Multiple myeloma (MM); Non-Hodgkin lymphoma (NHL) Memory B cell deficiency secondary to haematopoietic stem cell transplantation (HSCT) Other haematological malignancy	Specific conditions have been defined for data tracking purposes (A)
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a).	

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Justification for Evidence Category	<p>One small crossover study of 12 patients with CLL or NHL reported that the number of serious bacterial infections was significantly decreased ($p = 0.001$) in the months in which patients received IgG every three weeks for one year. Serious bacterial infections showed a trend to be associated with an IgG level <6.4 g/L.</p> <p>Three randomised controlled trials (RCTs) and one crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after three to four-weekly administration of IVIg for one year.</p> <p>One placebo-controlled RCT of monthly IVIg given to 82 MM patients for one year (with 22 withdrawing due to reaction) concluded that IVIg protects against life-threatening infections and significantly reduces risk of recurrent infections. The greatest benefit was seen in</p>	<p>One small crossover study of 12 patients with CLL or NHL reported that the number of serious bacterial infections was significantly decreased ($p = 0.001$) in the months in which patients received IgG every three weeks for one year. Serious bacterial infections showed a trend to be associated with an IgG level <6.4 g/L.</p> <p>Three randomised controlled trials (RCTs) and one crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after three to four-weekly administration of IVIg for one year.</p> <p>One placebo-controlled RCT of monthly IVIg given to 82 MM patients for one year (with 22 withdrawing due to reaction) concluded that IVIg protects against life-threatening infections and significantly reduces risk of recurrent infections. The greatest benefit was seen in individuals who had a poor response to pneumococcal vaccine. A small prospective RCT with 30 multiple myeloma patients reported a possible decrease in symptoms of chronic bronchitis.</p> <p>A recent systematic review and meta-analysis of patients undergoing HSCT [60 trials (>4000 patients)] reported an increased risk of veno-occlusive disease with no survival benefit particularly in studies conducted since 2000. The authors concluded that routine prophylaxis with IVIg is not supported, but suggest that its use may be considered in lymphoproliferative disorder patients with hypogammaglobulinaemia and</p>	<p>Justification for evidence was reviewed, literature search was undertaken and no changes made. (A)</p>

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	<p>individuals who had a poor response to pneumococcal vaccine. A small prospective RCT with 30 multiple myeloma patients reported a possible decrease in symptoms of chronic bronchitis.</p> <p>A recent systematic review and meta-analysis of patients undergoing HSCT [60 trials (>4000 patients)] reported an increased risk of veno-occlusive disease with no survival benefit particularly in studies conducted since 2000. The authors concluded that routine prophylaxis with IVIg is not supported, but suggest that its use may be considered in lymphoproliferative disorder patients with hypogammaglobulinaemia and recurrent infections, for reduction of clinically documented infections.</p>	<p>recurrent infections, for reduction of clinically documented infections.</p>	

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Description and Diagnostic Criteria	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria.	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria. A diagnosis of bronchiectasis or suppurative lung disease in patients on Ig therapy must be consistent with the 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),			Position statement from the Thoracic Society of Australia and New Zealand (TSANZ) and the Australian Lung Foundation was added to confirm the requirements for an eligible diagnosis of suppurative lung disease or bronchiectasis. (A)
Diagnosis is required		Yes	Which Speciality	Haematologist or General Physician or Paediatrician	Specialities of the Treating specialist was defined. (A)
Diagnosis must be verified		No	Which Specialty		
Exclusion Criteria	The following conditions should not be approved under this indication: 1. HIV in children (see page 185); 2. Transplantation-related immunomodulation (solid organ transplantation; (see page 208); 3. Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency (see page 106).	Solid organ transplantation B cell depletion therapy Thymoma-associated hypogammaglobulinaemia (Goods Syndrome) Transplantation-related immunomodulatory therapy (kidney and other solid organ transplantation).			Listed exclusions will refer queries to the appropriate section within the written version or the Ig system.

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Indication for use	<p>Prevention of recurrent bacterial infections due to antibody failure associated with haematological malignancies.</p> <p>Prevention of recurrent bacterial infections in patients undergoing HSCT for haematological malignancies.</p>	<p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with haematological malignancies.</p> <p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia post HSCT</p>	<p>Indication wording has largely been retained. The Indication for HSCT confirmed eligibility is only after HSCT has been completed and that HSCT does not need to be performed for haematological malignancy. HSCT is not unusual in children for non malignant reasons, these patients are cared for by haematologists and SWG recommends retention under the same condition to avoid confusion by prescribers. (A)</p>
Qualifying Criteria	<p>Diagnosis of acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation with:</p> <ul style="list-style-type: none"> Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein); <p>OR</p> <ul style="list-style-type: none"> Hypogammaglobulinaemia with IgG <4 g/L (excluding paraprotein). 	<p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with haematological malignancies.</p> <p>[Group 1]</p> <ul style="list-style-type: none"> Serum IgG less than the lower limit of the age related reference range measured on two separate occasions (excluding paraprotein). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. <p>AND</p> <p>[Group 2]</p> <ul style="list-style-type: none"> Patient has had one life-threatening bacterial infection (e.g. meningitis, sepsis) in the previous 12 months <p>OR</p> <ul style="list-style-type: none"> At least two serious infections in the last six months requiring more than standard courses of antibiotics (eg. Hospitalisation, intravenous or prolonged antibiotic therapy) 	<p>Diagnosis will be confirmed in the Ig system by selection of the specific condition above. (A)</p> <p>Eligibility criteria have been aligned with the other condition for secondary hypogammaglobulinaemia and now require testing of IgG on 2 separate occasions and the collection of baseline IgA and IgM levels. (A)</p> <p>For hypogammaglobulinaemia after HSCT - the same criteria apply.</p>

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	<p>Note: For data tracking purposes, the type of malignancy being treated should be recorded with each request for IVIg.</p>	<p>OR</p> <ul style="list-style-type: none"> • Patient has significant hypogammaglobulinemia with serum IgG <4g/L (excluding paraprotein) and information regarding the frequency and severity of infections requiring treatment in last 6 months must be provided. <p>Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.</p> <p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia post HSCT.</p> <p>[Group 1]</p> <ul style="list-style-type: none"> • The patient has undergone HSCT <p>AND</p> <ul style="list-style-type: none"> • Serum IgG less than the lower limit of the reference range measured on two separate occasions. Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. <p>AND</p> <p>[Group 2]</p> <ul style="list-style-type: none"> • One life-threatening bacterial infection (e.g. meningitis, sepsis) in the previous 12 months; <p>OR</p> <ul style="list-style-type: none"> • At least 2 serious infections in the last 6 months requiring more than standard courses of antibiotics (eg. hospitalisation, intravenous antibiotics or prolonged antibiotic therapy) <p>OR</p>	

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		<ul style="list-style-type: none"> • Patient has significant hypogammaglobulinaemia with serum IgG <4g/L (excluding paraprotein) and information regarding the frequency and severity of infections requiring treatment in last 6 months must be provided. <p>Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.</p>	
Review Criteria	<p>Six-monthly review to assess clinical benefit.</p> <p>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.</p> <p>Written confirmation from the treating physician that:</p> <ul style="list-style-type: none"> • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of 	<p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with haematological malignancies.</p> <p>Initial review is required at six months by a haematologist, general physician or paediatrician and ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.</p> <p>Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are normalising this may suggest recovery of the immune system.</p> <p>IVIg 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.</p> <p>On review of an authorisation period</p> <ul style="list-style-type: none"> • As 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 assessed. <p>AND</p> <ul style="list-style-type: none"> • A trial period of cessation of IVIg for the purposes of immunological 	<p>Review timeframes have been aligned with the other secondary hypogammaglobulinaemia condition for the initial review at 6 months and subsequent reviews annually. (A)</p> <p>Script added to indicate the relevance of IgA and IgM levels as being an indication for a normalising immune system and consideration for a trial off Ig therapy. Cessation should be considered every year unless contra-indicated. Contra-indication reasons have been defined. (A)</p> <p>If patients relapse, they are required to requalify for recommencement of Ig therapy.</p>

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	<p>IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds.</p> <p>In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.</p>	<p>evaluation will commence in September or October</p> <p>OR</p> <ul style="list-style-type: none"> A trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinemia persists where no significant improvement has occurred in the underlying condition). <p>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.</p> <p>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).</p> <p>Prevention of recurrent bacterial infection due to hypogammaglobulinemia post HSCT</p> <p>Initial review is required at six months by a Haematologist, General Physician or Paediatrician with subsequent reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.</p> <p>Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are normalising this may suggest recovery of the immune system. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical</p>	<p>The position statement from TSANZ and ALF has been referenced as a reminder of the diagnostic criteria for eligibility.</p> <p>Review periods and criteria post HSCT are consistent with the first indication.</p>

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		<p>and/or immunological evaluation before re-commencement of therapy.</p> <p>On review of an authorisation period</p> <ul style="list-style-type: none"> 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 assessed. <p>AND</p> <ul style="list-style-type: none"> A trial period of cessation of IVIg for the purposes of immunological evaluation will commence in September or October <p>OR</p> <ul style="list-style-type: none"> 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 hypogammaglobulinemia persists where no significant improvement has occurred in the underlying condition). <p>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.</p> <p>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).</p>	

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Dose	<p>Maintenance dose: 0.4 g/kg every four weeks, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range.</p> <p>Loading dose: One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L.</p> <p>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.</p> <p>Refer to the current product information sheet for further</p>	<p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with haematological malignancies</p> <p>Maintenance Dose - 0.4 g/kg every four weeks or more frequently to achieve an 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.</p> <p>Loading Dose - One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L.</p> <p>Chronic suppurative lung disease – 0.4g/Kg monthly or more frequently 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 4 week period which might be by divided doses more frequently than monthly.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p> <p>Prevention of recurrent bacterial infections due to hypogammaglobulinemia post HSCT</p> <p>Maintenance Dose - 0.4 g/kg every four weeks or more frequently to</p>	<p>Dosing is largely unchanged however, scripting has been added to define the upper dosing limit rather than allow unlimited increases to achieve IgG trough level. The Immunology SWG has advised that improved outcomes can be achieved with lower dose more frequent treatment to avoid very highs and then low IgG levels.</p> <p>Dosing allowances for chronic suppurative lung disease have been included to provide consistency with the other secondary hypogammaglobulinaemia indication.</p>

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	<p>information.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>	<p>achieve an 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.</p> <p>Loading Dose - One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L.</p> <p>Chronic suppurative lung disease – 0.4g/Kg monthly or more frequently 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 4 week period which might be by divided doses more frequently than monthly.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Refer to the current product information sheet for further information.</p>	

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