

## 2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia

<b>v2.1 CONDITION NAME:</b> Pyoderma gangrenosum (PG)	
<b>v3.0 CONDITION NAME:</b> Pyoderma gangrenosum	
<p><b>PROPOSED APPROACH:</b></p> <p><b>To retain Pyoderma gangrenosum in <i>Exceptional circumstances only</i> with the changes as outlined.</b></p>	<p><b>SUMMARY OF RATIONALE:</b></p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> <li>- Although not commonly prescribed, Ig therapy should remain as an option for use for patients with persistent severe PG as it is a rare condition that is potentially life threatening and associated with blindness, oesophageal strictures, scarring and fibrosis of the skin with alopecia, nail loss and mitten like deformities of the hands. There are few effective therapeutic modalities available.</li> <li>- The Australasian College of Dermatologists (Australian College of Dermatologists) has confirmed there is a role of Ig in the treatment of EBA and the criteria have been developed in consultation with this expert group.</li> <li>- Qualifying criteria have been developed to ensure the degree of severity and non-responsiveness to previous treatment or where such treatment is contraindicated or has resulted in unacceptable side effects or toxicity prior to commencing Ig therapy.</li> <li>- Review criteria require continual improvement to be demonstrated in ulcer healing for ongoing access to Ig therapy, with a trial off Ig treatment once all ulcers are showing signs of healing.</li> <li>- This condition is included as a 'grey' or low priority in the Clinical Guidelines for Ig Use of the United Kingdom (UK Department of Health, 2011). It is not listed in the Canadian National IVIg Utilisation Management Guidelines (Ontario Regional Blood Coordinating Network, 2016) although it is understood that local provincial funders may still approve rare conditions.</li> </ul>
<b>v2.1 CONDITION CATEGORY:</b> Condition for which Ig use is in exceptional circumstances only (Chapter 7)	
<b>v3.0 CONDITION CATEGORY:</b> Condition for which Ig use is in exceptional circumstances only (Chapter 7)	

**Role of Ig therapy:** Ig should be used where possible as an adjuvant therapy in conjunction with other immunosuppressive therapy where resistance to such therapy and biological agents has been demonstrated. Ig therapy is regarded as adjuvant therapy and is considered third or fourth line treatment after alternative therapies have been unsuccessful in achieving improvement or remission. It can then enhance the effect of existing treatment rather than as monotherapy. In addition, the safety profile of Ig means that it is useful when additional efficacy is required without increasing levels of immunosuppression. Trials off Ig therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Ig treatment can be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
<b>Condition Name</b>	Pyoderma Gangrenosum	Pyoderma Gangrenosum	Unchanged
<b>Specialty</b>	Immunology	Immunology	Unchanged
<b>Category</b>	<i>Exceptional circumstances only</i>	<i>Exceptional circumstances only</i>	Unchanged
<b>Specific Conditions</b>		Pyoderma Gangrenosum	
<b>Level of Evidence</b>	Insufficient data ( <a href="#">Category 4a</a> ).	Insufficient data (Category 4a)	Unchanged
<b>Justification for Evidence Category</b>		Ig therapy is regarded as adjuvant treatment and is considered third or fourth line treatment, after alternative therapies have been unsuccessful in achieving improvement or remission. While Ig has been proven to be effective in small case series (Patel et al, 2015 and Cummins et al, 2007) and case reports (Cafardi et al, 2014 and De Zwaan et al, 2009), ideally it is used to enhance the effect of existing treatment, rather than as monotherapy.	This section has been drafted following assessment of the literature and consultation with the Australian College of Dermatologists.

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<b>Indication</b>		<p><b>Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects.</b></p> <p><b>Relapse of PG in previously responding patients following a trial off Ig therapy</b></p>	<p>Two indications have been defined; the second to support recommencement of Ig therapy in responding patients that may relapse once treatment has been ceased.</p>
<b>Description and Diagnostic Criteria</b>		<p>Pyoderma gangrenosum (PG) is a chronic inflammatory disease characterised by painful skin ulcerations with raised erythematous and undermined borders. The aetiology is 'not well understood but is generally considered to be an aberrant immune response characterised by a dermal neutrophilic infiltrate' (Patel et al, 2015) responding to immunosuppressant medication and sometimes presenting in patients treated with immune modifying medications such as Granulocyte - colony stimulating factor. The condition is recognised to occur more commonly in patients with immune mediated diseases including Inflammatory bowel disease, inflammatory arthritis, and haematological diseases (myelodysplastic syndrome, multiple myeloma, polycythaemia vera, leukaemia).</p> <p>A clinical diagnosis of exclusion is required as there are no clear serologic or histological criteria.</p> <p>While trauma from surgery may exacerbate ulceration, traditional wound care including compression, debridement, and skin grafting may be options for slow healing ulcers that are entirely devoid of an inflammatory border. The persistence of an ulcer does not indicate non-responsiveness to immunosuppressant medications given that they will take time to heal following successful suppression of the aberrant pathogenic immune response. In addition, oedema may be induced by immunosuppressant</p>	<p>This section has been drafted following assessment of the literature and consultation with the Australian College of Dermatologists.</p>

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		medication and inhibit wound healing and/or bacterial colonisation can delay wound healing in a patient otherwise appropriately immunosuppressed. A residual poorly healing, but non-inflammatory ulcer does not require additional immunosuppression and should be distinguished from an active inflammatory PG ulcer. Ig should be reserved for severe cases when treatment with combinations of immunosuppressants and also biological agents has been either ineffective or unable to be tolerated due to severity of side effects or contraindications. The safety profile of Ig means that it is useful when additional efficacy is required, without increasing levels of immunosuppression. Nevertheless, given the expense of Ig careful consideration should be given when considering its usage.			
Diagnosis is required		Yes	By which specialty	Dermatologist Clinical immunologist	Diagnosis is now required by a dermatologist or a clinical immunologist as these specialties manage patients with this rare condition.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria	Use of intravenous immunoglobulin (IVIg) is limited to patients with significant pyoderma gangrenosum, diagnosed by a Dermatologist, unresponsive to corticosteroids and other immunosuppressive	<b>Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects.</b> <ul style="list-style-type: none"> <li>• Severe PG with large or persistent ulceration causing significant impact on quality of life</li> </ul> AND			Qualifying criteria have been developed in consultation with the Australian College of Dermatologists. An assessment of the patient's quality of life is required as well as the size and

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	agents.	<ul style="list-style-type: none"> <li>• Unresponsive to a trial of oral corticosteroid therapy for at least 6 weeks</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Corticosteroid therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Unresponsive to a trial of immunosuppressant therapy in combination with prednisolone for at least eight weeks</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Immunosuppressant medication is contraindicated or has resulted in unacceptable side effects or significant toxicity</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Unresponsive to a trial of biologic therapy for at least 3 months</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Biologic therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity or is unavailable</li> </ul> <p><b>Relapse of PG in previously responding patients following a trial off Ig therapy</b></p> <ul style="list-style-type: none"> <li>• Worsening in at least four of the following measures in the majority of ulcers in a previously responding patient               <ul style="list-style-type: none"> <li>- increase in the depth of violaceous colour at ulcer edge.</li> <li>- increase in size</li> </ul> </li> </ul>	<p>persistence of ulcers.</p> <p>Criteria confirm that the patient has been unresponsive to at least six weeks' treatment with corticosteroids and a further eight week trial of cyclosporin with prednisolone, mycophenolate mofetil with prednisolone, methotrexate with prednisolone or azathiaprine with prednisolone.</p> <p>A three month trial of biologic such as Infliximab, Adalimumab, Etanercept or Ustekinumab is also required prior to commencing Ig therapy.</p>

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		<ul style="list-style-type: none"> <li>- increase in depth</li> <li>- increase in undermining of edges</li> <li>- increase in slough</li> <li>- reduction in granulation tissue</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Despite treatment with corticosteroids and at least one Immunosuppressant or biological agent</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Corticosteroids and/or Immunosuppressant and/or biologic agents are contraindicated or resulted in unacceptable side effects or significant toxicity</li> </ul>	
<p><b>Review Criteria</b></p>		<p><b>Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects.</b></p> <p>Review by a Dermatologist or Clinical Immunologist is required within 3 months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> <p><b>On review of the initial authorisation period</b></p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Improvement in at least four of the following six measures in the majority of ulcers compared to at qualifying</li> </ul>	<p>Review periods and criteria have been defined in consultation with Australian College of Dermatologists.</p> <p>At each review, evidence of improvement / healing in the majority ulcers must continue to be demonstrated for the patient to have access to continuing Ig therapy.</p>

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		<p>assessment:</p> <ul style="list-style-type: none"> <li>- reduction in the depth of violaceous colour at ulcer edge.</li> <li>- reduction in size</li> <li>- reduction in depth</li> <li>- reduction in undermining of edges</li> <li>- reduction in slough</li> <li>- increase in granulation tissue</li> </ul> <p><b>On review of a continuing authorisation period</b></p> <p>For stable patients on maintenance treatment, review by Dermatologist or Clinical Immunologist is required every six months.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Further improvement in ulcer(s)</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Once disease activity is controlled by evidence of healing/ improvement in <i>all</i> ulcers, a trial off therapy should be considered</li> </ul> <p>A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these</p>	<p>The conditions for trialling off Ig therapy have been defined.</p>

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		<p>measures.</p> <p><b>Relapse of PG in previously responding patients following a trial off Ig therapy</b></p> <p>Review by a Dermatologist or Clinical Immunologist is required within 3 months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned. For patients on maintenance therapy, six monthly review is required.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> <p><b>On review of the initial authorisation period</b></p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Improvement in at least four of the following six measures in the majority of ulcers compared to at qualifying assessment: <ul style="list-style-type: none"> <li>- reduction in the depth of violaceous colour at ulcer edge</li> <li>- reduction in size</li> <li>- reduction in depth</li> <li>- reduction in undermining of edges</li> <li>- reduction in slough</li> <li>- increase in granulation tissue</li> </ul> </li> </ul> <p><b>On review of a continuing authorisation period</b></p>	



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		<p>For stable patients on maintenance treatment, review by Dermatologist or Clinical Immunologist is required every six months.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Further improvement in ulcer(s)</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Once disease activity is controlled by evidence of healing/ improvement in all ulcers, a trial off therapy should be considered</li> </ul> <p><b>A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.</b></p>	
<b>Dose</b>	<p>Induction dose: 2 g/kg divided over three days.</p> <p>Maintenance therapy: 1–2 g/kg divided over two days, monthly for 4–6 months.</p> <p>IVIg should be ceased in patients who fail to respond after three cycles.</p>	<p><b>Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects.</b></p> <p><b>Initial Dose</b>– 2 g/kg in divided dose over 3 days, followed by two further monthly treatments of 1-2 g/kg</p> <p><b>Maintenance Dose</b> – 0.5 to 2 g/kg in single or divided doses 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 has been defined with three months’ treatment at 2 g/kg to determine whether there has been a clinical response and then commencement on maintenance therapy. A range in maintenance dose is provided to support the weaning of patients from Ig treatment.</p>

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	<p>Refer to the current product information sheet for further information.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>	<p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> <p><b>Relapse of PG in previously responding patients following a trial off Ig therapy</b></p> <p><b>Initial Dose</b>– 2 g/kg in divided dose over 3 days, followed by two further monthly treatments of 1-2 g/kg</p> <p><b>Maintenance Dose</b> – 0.4 to 2 g/kg in single or divided doses monthly.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p>	
<p><b>References</b> (most recent update: August 2016)</p>			

Cafardi J and Sami N (2014) Intravenous immunoglobulin as salvage therapy in refractory pyoderma gangrenosum: report of a case and review of the literature. *Case Reports Dermatology*, 6(3):239-44.

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**POTENTIAL OPERATIONAL IMPACT**

There may be some operational impacts as a result of these changes, if patients are not currently treated with alternative therapies (as recommended by Australian College of Dermatologists) prior to commencing Ig therapy. While there will be some data entry required at initial Ig request and review, the clinical assessments are largely presented as drop down menus and short descriptions so as not to be burdensome. The requirement to demonstrate a clinical response after three months' treatment may be a new requirement for new patients in the future. The need to consider a trial off Ig therapy once evidence of healing is achieved in all ulcers is expected to be supported given that relapsing (responding) patients are likely to be eligible to recommence treatment in due course.

**POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE**

**Description of impact on patients:**

These criteria have been developed in consultation with Australasian College of Dermatologists who have advised that Ig therapy is only required in the most severe cases. There are a number of treatments that are available for this condition, and Ig therapy is only used after patients have not responded to other treatments (unless they are unavailable or inappropriate) and Ig should be used in combination with other medications rather than on its own, as this approach has been proven to improve ulcer healing. The aim of treatment is to achieve improvement and healing in all ulcers.

The formal access criteria now proposed for this condition require that either a dermatologist or a clinical immunologist makes the diagnosis and manages the ongoing treatment. This is because this is a rare condition requiring a number of different medications to be used and it is important that the correct treatment is being given to patients.

Existing patients will already be regularly reviewed by their dermatologist or clinical immunologist so the requirement for six monthly checks to confirm that Ig combination therapy is effective in improving ulcer healing will not place an added burden on patients. If patients are not receiving Ig therapy in combination with another medication, a second agent will be commenced, unless side effects or toxicity limit this requirement. Once disease activity is stable with healing or improvement in all ulcers, doctors will consider a trial of reducing dose and then stopping Ig therapy. A different medication will then be substituted for the Ig therapy. If patients relapse once Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.

For new patients authorised for Ig therapy, an initial check after three months treatment is required to confirm that the Ig therapy is helping to heal the ulcers. If ulcers have not improved after this time, Ig therapy will be ceased and substituted with a different treatment approach. If improvement has been demonstrated, Ig therapy will continue with six monthly checks on progress to ensure that ulcers are continuing to improve. These can be performed as part of the usual monitoring process. If ulcers are not continuing to show signs of improvement and healing, Ig therapy will be substituted with a different medication. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months' treatment and when there is evidence of healing and /or improvement in all ulcers. A different medication will then be substituted for the Ig therapy. If patients relapse once Ig treatment has been

		stopped, a further request to restart ongoing Ig therapy can be made.				
<b>Impact on demand:</b>		Ig use has increased slightly over the last three years, however, it is unknown as to whether clinical practice is aligned with the approach outlined in the revised <i>Criteria</i> . It is noted that in 2015/16, Ig use was limited to three states only. It is possible that the introduction of specific qualifying and review criteria with the requirement for trialling off may be a change, which may result in a reduction in use. However, given the relatively low level of demand, it is unlikely to impact overall Ig usage to any great extent. It is acknowledged that the approach to require trialling off of patients from Ig therapy once all ulcers are showing improvement or signs of healing is likely to eliminate ongoing long term Ig use in existing patients.				
	2011-12	2012-13	2013-14	2014-15	2015-16	The Specialist Working Group estimated magnitude of effect: Marginal: <\$500K reduction against projected demand
Patient number	0	10	23	26	27	
Total Grams issued	0	4,223	8,935	13,256	16,598	
% Total Grams issued		0.12%	0.22%	0.3%	0.33%	
<b>Specialist Working Group knowledge development opportunities and recommendations</b>						
None identified at this time.						
<p><b>END OF PUBLIC CONSULTATION DOCUMENT</b></p> <p><b>Next review: Eighteen months following implementation of BloodSTAR v3.0</b></p>						