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	**Pemphigus vulgaris (PV)**	**Pemphigus vulgaris (PV)**	
Specialty	Dermatology	Dermatology	
Chapter	6	6	
Specific Conditions			
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a).	Evidence of probable benefit – more research needed (Category 2a).	Unchanged
Description and Diagnostic Criteria	PV is a rare but potentially fatal condition accounting for approximately 70% of pemphigus cases. While the cause is unknown, an immuno-genetic predisposition is well established. PV may also be drug-induced. Drugs reported to be most significantly associated with PV include penicillamine, captopril and other thiol-containing compounds. Rifampicin and emotional stress have recently been reported as triggers for PV. The oral cavity is almost always affected and erosions can be scattered and extensive, with subsequent dysphagia. Blistering and erosions	PV is a rare but potentially fatal condition accounting for approximately 70% of pemphigus cases. While the cause is unknown, an immuno-genetic predisposition is well established. PV may also be drug-induced. Drugs reported to be most significantly associated with PV include penicillamine, captopril and other thiol-containing compounds. Rifampicin and emotional stress have recently been reported as triggers for PV. The oral cavity is almost always affected and erosions can be scattered and extensive, with subsequent dysphagia. Blistering and erosions	Unchanged – endorsed by the College of Dermatology

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	secondary to the rupture of blisters may be painful and limit the patient's daily activities. Pemphigus may occur in patients with other autoimmune diseases, particularly myasthenia gravis and thymoma. **Prognosis** The severity and natural history of PV are variable. Before the advent of steroids, most patients with PV died. Treatment with systemic steroids has reduced the mortality rate to 5–15%. Most deaths occur during the first few years of disease and if the patient survives five years, the prognosis is good. Early disease is easier to control than widespread disease and mortality may be higher if therapy is delayed. Morbidity and mortality are related to the extent of disease, the maximum dose of corticosteroid required to induce remission, and the presence of other diseases.	secondary to the rupture of blisters may be painful and limit the patient's daily activities. Pemphigus may occur in patients with other autoimmune diseases, particularly myasthenia gravis and thymoma. **Prognosis** The severity and natural history of PV are variable. Before the advent of steroids, most patients with PV died. Treatment with systemic steroids has reduced the mortality rate to 5–15%. Most deaths occur during the first few years of disease and, if the patient survives five years, the prognosis is good. Early disease is easier to control than widespread disease, and mortality may be higher if therapy is delayed. Morbidity and mortality are related to the extent of disease, the maximum dose of corticosteroid required to induce remission, and the presence of other diseases.	
Justification for Evidence Category	In a retrospective cohort study, 15 corticosteroid-dependent patients with moderate to severe PV were treated with IVIg and followed over a mean period of 6.2 years. All 15 patients had a	In a retrospective cohort study, 15 corticosteroid-dependent patients with moderate to severe PV were treated with intravenous immunoglobulin (IVIg) and followed over a mean period of 6.2	Revised to include a 2009 RCT which supports the current level of evidence. (A)

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	satisfactory clinical response to IVIg therapy. IVIg had a demonstrable corticosteroid-sparing effect and was considered a safe and effective alternative treatment in patients who were dependent on systemic corticosteroids or who developed significant adverse effects as a result of their use (Biotext 2004).	years. All 15 patients had a satisfactory clinical response to IVIg therapy. IVIg had a demonstrable corticosteroid-sparing effect and was considered a safe and effective alternative treatment in patients who were dependent on systemic corticosteroids or who developed significant adverse effects as a result of their use (Biotext 2004). A 2009 (Amagai et al 2009) small randomised controlled trial (RCT) for pemphigus vulgaris and foliaceus patients (61 patients in total) supports both safety and efficacy of Ig treatment.			
Diagnosis is required	Moderate to severe disease diagnosed by a dermatologist;	Yes	Which Speciality	Dermatologist or Clinical Immunologist	Clinical Immunologist added following public consultation feedback.
Diagnosis must be verified			Which Specialty		
Exclusion Criteria					
Indication for use	Moderate to severe PV as an adjuvant to prolonged corticosteroid treatment.	**Moderate to severe PV as an adjuvant to prolonged corticosteroid treatment.**			
Qualifying Criteria	Moderate to severe disease diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated;	• Moderate to severe PV disease, including widespread oral lesions, laryngeal involvement and/or erosions in skinfolds (vegetans) proven by autoantibody testing and/or biopsy. AND • Persistent disease despite standard			Qualifying criteria with evidence items have been defined. It is recognised that not all patients have demonstrable autoantibodies, however all patients will have a biopsy (A) Alternative therapies to Ig include: i. Corticosteroids ii. Azathioprine iii. Methotrexate iv. Mycophenolate

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	OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.	corticosteroid and immunosuppressant therapy of steroids and at least two immunosuppressant agents or Rituximab. OR • Severe side effects prohibit the continuation of corticosteroids and immunosuppressant agents. OR • Corticosteroids and/or immunosuppressant agents are contraindicated.	v. Rituximab Severe immunosuppressant side effects include: i. Significant infection including sepsis ii. Malignancy iii. Marrow suppression and cytopenia iv. Unstable Diabetes v. Severe osteoporosis vi. History of avascular necrosis Contraindication Reasons include: i. Significant infection including sepsis ii. Malignancy iii. Marrow suppression and cytopenia iv. Unstable Diabetes v. Severe osteoporosis vi. History of avascular necrosis
Review Criteria	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Titres of serum antibodies against keratinocytes. • Whether systemic corticosteroids can be gradually discontinued. • Total dose and duration of corticosteroid therapy, and number of relapses before and after the initiation of IVIg therapy.	Review is required every six months by a Dermatologist or Clinical Immunologist and improvement must be demonstrated for continuation of supply. **On review of an initial authorisation period** • Response to Ig therapy has been demonstrated by a reduction in the number and severity of lesions compared to the qualifying value **On review of a continuing authorisation period**	Review criteria with evidence items to determine response are defined. While antikeratinocyte antibody titre will be monitored if present, a description of the clinical response to Ig therapy and a reduction in severity of lesions will constitute a response. (A)

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		• Response has been demonstrated by a reduction in the number and severity of lesions compared to previous review, but there is remaining activity or stable disease AND • A trial-off Ig therapy is planned or, if not planned, a reason is provided. AND • If continuing Ig therapy, a reduction in dose is planned or, if not planned, a reason is provided. Consideration should be given to a trial-off Ig therapy once the patient has achieved stabilised disease or clinical remission. The minimal effective dose should be prescribed.	
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **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**	**Maintenance Dose** - Efficacy is demonstrated with doses of at least 2 g/kg per monthly treatment cycle. Consideration should be given to a trial-off immunoglobulin (Ig) therapy once the patient has achieved stabilised disease or clinical remission. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	Dosing is unchanged. Script added. (A)

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	that achieves the appropriate clinical outcome for each patient.	Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	

BIBLIOGRAPHY

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