### 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** | **PROPOSED REVISIONS TO THE CRITERIA** | **SWG RATIONALE FOR PROPOSED CHANGE****(A) Administrative)****(B) Progressive** **(C) Programmed** |
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| **Condition Name** | **Pemphigus foliaceus (PF)** | **Pemphigus foliaceus (PF)** |  |
| **Specialty** | Dermatology | Dermatology |  |
| **Chapter** | 6 | 6 |  |
| **Specific Conditions** |  | Pemphigus erythematosusPemphigus herpetiformisEndemic pemphigus foliaceusIgA pemphigus foliaceusParaneoplastic pemphigus foliaceusDrug-induced pemphigus foliaceus | Specialist Working Group (SWG) and College of Dermatology recommend that these specific conditions are eligible. (A)  |
| **Description and Diagnostic Criteria** | PF is a rare autoimmune blistering skin disease characterised by loss of cohesion of cells (acantholysis) in the superficial (subcorneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in pemphigus vulgaris). It is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis.The disease has a long-term course with patients maintaining satisfactory health. Spontaneous remissions occasionally occur. | PF is a rare autoimmune blistering skin disease characterised by loss of cohesion of cells (acantholysis) in the superficial (subcorneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in pemphigus vulgaris). It is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis.The disease has a long-term course with patients maintaining satisfactory health. Spontaneous remissions occasionally occur. | Unchanged.  |
| **Level of Evidence** | Small case studies only; insufficient data ([Category 4a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). | Evidence of probable benefit – more research needed. ([Category 2a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). | SWG and College of Dermatology recommend that level of evidence should be changed to Category 2a. (A)  |
| **Justification for Evidence Category** | Habif (2004) concluded that IVIg was effective as monotherapy for PF and particularly useful in patients who experienced life-threatening complications from immunosuppression. Sami et al (2002) observed that autoantibody titres to desmoglein 1 in a series of 15 PF patients declined persistently following IVIg therapy. | Habif (2004) concluded that intravenous immunoglobulin (IVIg) was effective as monotherapy for PF and particularly useful in patients who experienced life-threatening complications from immunosuppression. Sami et al (2002) observed that autoantibody titres to desmoglein 1 in a series of 15 PF patients declined persistently following IVIg therapy.Amagai M et al conducted a small randomised controlled trial (RCT) in 2009 for pemphigus vulgaris and foliaceus patients (61patients in total) that supported both safety and efficacy of Ig therapy.  | This section was reviewed and revised. A small RCT was added supporting a change in evidence level. (A) |
| **Diagnosis is required** |  Severe widespread PF, defined as disease involving 30% or more of body surface area, diagnosed by a dermatologist; | Yes | Which Speciality | DermatologistImmunologist | Unchanged  |
| **Diagnosis must be verified** |   | No | Which Specialty |  |  |
| **Exclusion Criteria** |  |  |  |
| **Indication for use** | PF resistant to corticosteroids and immunosuppressive therapy or when these agents are contra-indicated. | **PF resistant to corticosteroids and immunosuppressive therapy or when these agents are contraindicated.** | Unchanged  |
| **Qualifying Criteria** | Severe widespread PF, defined as disease involving 30% or more of body surface area, diagnosed by a dermatologist;AND1. Corticosteroids or immunosuppressive agents are contraindicated;

OR1. Condition is unresponsive to corticosteroids and immunosuppressive agents;

OR1. Presenting with severe side effects of therapy.
 | * Severe widespread proven PF disease involving at least 30% body surface, positive direct immunofluorescence test and autoantibody titre

AND* Persistent disease despite standard corticosteroid and immunosuppressant therapy using Rituximab or two alternative immunosuppressant agents.

OR* Persisant disease and severe side effects prohibit the continuation of corticosteroids and immunosuppressant agents.

OR* Persistant disease and corticosteroids and/or immunosuppressant agents are contraindicated.
 | Qualifying criteria requiring confirmation of diagnosis and evidence items to be tracked to determine response have been defined. (A) Options for immunosuppressive therapy are 1. Corticosteroids
2. Azathioprine
3. Methotrexate
4. Mycophenolate
5. Rituximab

Values for severe immunosuppressant side effects include1. Significant infection including sepsis
2. Malignancy
3. Marrow suppression and cytopenia
4. Unstable Diabetes
5. Severe osteoporosis
6. History of avascular necrosis

(A)  |
| **Review Criteria** | * Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply.
* Clinical progression: Treatment is stopped when patients are clinically free from disease and have a negative finding on direct immunofluorescence.
* Autoantibody titres reflect the response to systemic therapy.
 | Review is required every six months by a Dermatologist and improvement must be demonstrated for continuation of supply. Autoantibody titres reflect the response to systemic therapy.**On review of an authorisation period*** Response to immunoglobulin (Ig) therapy is demonstrated by a reduced percentage of body surface area affected compared to the qualifying value.

AND * The autoantibody titre is reduced.

AND * Patients qualify for further treatment if the direct immunofluorescence test remains positive.

Clinical progression: treatment is stopped when patients are clinically free from disease and have a negative finding on direct immunofluorescence. | Review criteria and evidence items have been defined. (A) Review is conducted six monthly. Autoantibody Titre is a direct correlator to disease severity, but more so as a marker for control of disease with treatment. Cessation of treatment is defined. (A)  |
| **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 that achieves the appropriate clinical outcome for each patient.** | **Maintenance** - Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle.The aim should be to use the lowest dose possible 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. | Dosing unchanged |

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| **BIBLIOGRAPHY** |
| Habif TP. Vesicular and bullous diseases. Chapter 16 in: Clinical Dermatology [electronic resource] : A Color Guide to Diagnosis and Therapy, 4th edition. Mosby Inc, Edinburgh. 2004Sami, N, Bhol, KC & Razzaque, A 2002, ‘Influence of IVIg therapy on autoantibody titres to desmoglein 1 in patients with pemphigus foliaceus’, *Clinical Immunology,* vol. 105, no. 2 pp. 192–8. |
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