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

| **v2.1 CONDITION NAME: Catastrophic anti-phospholipid syndrome** |
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| **PROPOSED APPROACH:****To retain Catastrophic anti-phospholipid syndrome in *Exceptional circumstances only* with the changes as outlined.**  | **SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that*:* * **Catastrophic anti-phospholipid syndrome** is a very rare and life-threatening condition with 40% mortality and Ig therapy becomes part of first line therapy (in combination with steroids and anti-coagulation) when plasmapheresis may be unavailable (e.g. rural hospitals, after hours), contraindicated or is unsuccessful in achieving a response.
* Given the rarity of this condition, the evidence level is unlikely to ever extend beyond case reports and series, however a mechanism of action for Ig therapy is reported to have been proven (Cervera et al, 2016).
* This condition is listed as low priority in times of shortage or a ‘grey’ condition in the UK NHS immunoglobulin guidelines (UK Department of Health, 2011) which is equivalent to conditions for exceptional use in Australia. It is not listed in the national Canadian IVIg Utilisation Management guidelines (Ontario Regional Blood Coordinating Network, 2016), however, it is understood that in both countries, that rare conditions may still be funded at the local (province or trust) level.
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| **v2.1 CONDITION CATEGORY: Condition for which Ig use is in** exceptional circumstances only (Chapter 7)**v3.0 CONDITION CATEGORY: Condition for which Ig use is in** exceptional circumstances only (Chapter 7) |
| **Role of Ig therapy:** Although patients with **Catastrophic anti-phospholipid syndrome** represent less than 1% of all patients with Anti-phospholipid syndrome, the situation is usually life-threatening with mortality of up to 40%. First line treatment in acute presentation includes steroids, plasmapheresis and anti-coagulation, however where plasmapheresis in not available or is contraindicated or where there is a deterioration after treatment with plasmapheresis, Ig therapy is indicated. It is acknowledged that plasmapheresis may not always be accessible in rural hospitals and other problems may arise in more populated locations such as a lack of trained staff or access after-hours.The mechanism of action of Ig therapy in this condition is reported to have been proven recently as acting to decrease anti-phospholipid antibody levels and therefore reducing the thrombotic risk by reducing pro-inflammatory levels in these patients. (Cervera et al, 2016)  Ig therapy is not indicated for chronic recurrent thrombosis, and this has been added as an exclusion criterion. |

| **ITEM** | **CRITERIAv2.1**  | **PROPOSED REVISIONS TO THE CRITERIA** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | Catastrophic antiphospholipid syndrome | Catastrophic anti-phospholipid syndrome | No change |
| **Specialty** | Immunology | Immunology  | No change |
| **Category**  | *Exceptional circumstances only*  | *Exceptional circumstances only* | No change |
| **Specific Conditions** | Catastrophic antiphospholipid syndrome | Catastrophic anti-phospholipid syndrome | No change |
| **Level of Evidence** | Insufficient data ([Category 4a](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-4a)). |  Insufficient data (Category 4a) | No change |
| **Justification for Evidence Category** |   | Given the rarity of this condition, the evidence level is unlikely to extend beyond case reports and series. An international registry of patients with Catastrophic APS (Cervera et al, 2016)was established in 2000 by the European Forum on anti-phospholipid antibodies and contains data from around 400 patients. Retrospective data analysis demonstrates that patients treated by plasmapheresis and Ig therapy demonstrate superior clinical outcomes.  | Justification for recommendation added.  |
| **Indication** | Intravenous immunoglobulin (IVIg) may be appropriate therapy for catastrophic antiphospholipid syndrome, a term that describes the accelerated form of antiphospholipid syndrome characterised by widespread small vessel thrombosis leading to multi-organ failure. It is not indicated for the treatment of antiphospholipid syndrome in other cases. Please see Antiphospholipid syndrome (non-obstetric) in Chapter 8 and Recurrent foetal loss (with or without antiphospholipid syndrome) in Chapter 8.  | **Confirmed diagnosis of CAPS with clinical deterioration post conclusion of steroid and plasmapheresis therapy or where therapies are contraindicated or plasmapheresis in not available.** | The Specialist Working Group drafted a more clearly defined indication after consideration of the literature which confirmed the role of plasmapheresis in the management of CAPS.  |
| **Description and Diagnostic Criteria** |   | Catastrophic anti-phospholipid syndrome (CAPS) describes a rare accelerated form of anti-phospholipid lipid syndrome characterised by widespread small vessel thrombosis leading to multi-organ failure. Occurring twice as often in women than men, diagnosis is demonstrated by clinical evidence of multiple organ involvement within 7 days; histopathological evidence of multiple small vessel occlusions, and laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titre. Although patients with catastrophic APS represent less than 1% of all patients with APS, the situation is usually life-threatening with mortality up to 40%. Optimal treatment uses steroids, plasmapheresis and anti-coagulation, however where plasmapheresis in not available or is contraindicated or where there is a deterioration after plasmapheresis, 2 g/kg Ig therapy over 5 days is indicated. Ig therapy is not indicated for chronic recurrent thrombosis, however, Rituximab has been shown to be effective in some individuals.  | New text added after consideration of the literature.  |
| **Diagnosis is required** |   | Yes | By which specialty | Immunologist Haematologist  | The Specialist Working Group advised that diagnosis is required by a clinical immunologist or a haematologist as this condition is most commonly managed by these specialists.  |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |   | Chronic recurrent thrombosis |  ‘Chronic recurrent thrombosis’ has been added as an exclusion criteria to distinguish it from CAPS as patients present with thrombosis in both conditions. Ig is not supported for chronic recurrent thrombosis.  |
| **Qualifying Criteria** | A patient will qualify for IVIg when all the following criteria are met: Evidence of rapidly evolving thrombosis involving two or more organsUnequivocal laboratory evidence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or beta 2 glycoprotein I antibodies)Other causes of thrombotic microangiopathy are considered less likely.Confirmation by histopathology of thrombotic small vessel occlusion in at least one organ or tissue is desirable but should not delay IVIg therapy if indicated. | * Rapidly evolving thrombosis involving three or more organs within seven days

AND* Laboratory evidence of antiphospholipid antibodies (at least one of anti-cardiolipin, beta 2 glycoprotein I antibody or lupus anticoagulant)

AND* Inadequate response to steroid therapy and plasmapheresis or a clinical deterioration post plasmapheresis

OR* Plasmapheresis is unavailable

OR* Plasmapheresis is contraindicated
 | Qualifying criteria developed and added based on the findings of the literature review and Specialist Working Group consensus. The Specialist Working Group noted that plasmapheresis may not always be accessible.  |
| **Review Criteria** |   | Review is not mandated for this condition. Clinical effectiveness of Ig therapy can be demonstrated by: • Survival | Given that Ig is one-off treatment in this setting, review is not mandated, however outcome measures have been defined including requesting a description of the clinical response to Ig therapy. The Specialist Working Group discussion noted the importance of gathering data on rare conditions to inform the future review of *the Criteria* for access and to demonstrate the benefit of Ig therapy. It was noted that it would be useful to dedicate resources to the follow-up of prescribers to record outcome information in future.  |
| **Dose** | Confirmation by histopathology of thrombotic small vessel occlusion in at least one organ or tissue is desirable but should not delay IVIg therapy if indicated.A single treatment is usually sufficient, based on a dose of 2 g/kg divided over 2–5 days. The potential pro-thrombotic effect of IVIg should be considered in this indication.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. | **Induction Dose –** 2 g/kg over 5 days Retreatment may be required in early relapse or occurrence of a second episode. 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 on dose, administration and contraindications.** | Dosing is unchanged and advice is provided regarding when re-treatment is indicated. . |

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| **References****(most recent update: April 2016)** |
| Asherson RA, Cervera R, de Groot PG, Erkan D, Boff, MC, Piette JC, Khamashta MA and Shoenfeld Y (2003) Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*, 12:530–34.<https://www.ncbi.nlm.nih.gov/pubmed/12892393>Asherson RA, Espinosa G, Cervera R, Font J and Reverter JC (2002) Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment. *Journal of Clinical Rheumatology*, 8(3):157–65.<https://www.ncbi.nlm.nih.gov/pubmed/17041346>Berman H, Rodriguez-Pinto I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al (2013) Rituximab use in catastrophic antiphospholipid syndrome: Descriptive analysis of the CAPS registry patients receiving rituximab. *Autoimmunity Reviews*, 12:1085-1090. <https://www.ncbi.nlm.nih.gov/pubmed/23777822>Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gomez-Puerta JA, Ramos-Casals M, et al (2006) Mortality in the Catastrophic Antiphopholipid syndrome. *Arthritis & Rheumatism*, 54:2568-2576.<https://www.ncbi.nlm.nih.gov/pubmed/16868979>Cervera R (2012) The Catastrophic Antiphospholipid Syndrome. [online]. Available at: <https://ontocrf.grupocostaisa.com/es/web/caps/contents>.Cervera R (2016). *Anti-phospholipid syndrome in systemic autoimmune diseases.* Second Edition. Elsevier, pp. 249.Cervera R, Asherson RA and Font J (2006) Catastrophic antiphospholipid syndrome. *Rheumatic Disease Clinics of North America*, 32(3):575–90.<http://www.karger.com/Article/Abstract/93565>Erkan D (2006) Therapeutic and prognostic considerations in catastrophic antiphospholipid syndrome. *Autoimmunity Reviews*, 6(2):98–103.<https://www.ncbi.nlm.nih.gov/pubmed/17138252>Espinosa G and Cervera R (2010) Antiphospholipid syndrome: frequency, main causes and risk factors of mortality. *Nature Reviews: Rheumatology*, 6:297- 300.<https://www.ncbi.nlm.nih.gov/pubmed/20386563>Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/.UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/216671/dh\_131107.pdfUK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster\_v4\_February2016.pdf |

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| **POTENTIAL OPERATIONAL IMPACT** |
| There is not anticipated to be any operational impact as a result of these changes. Any relapse is likely to occur after 6 months and patients would need to re-qualify for Ig treatment, when necessary.  |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | Given that treatment is short lived to manage any acute episode, these criteria are anticipated to align with current clinical practice and will support the ongoing treatment of any existing patients requiring treatment at the time of implementation, should that be required. As a result, there is not expected to be any impact on patients as a result of these changes. Treatment of acute episodes involves a number of therapies used in combination to stop the clotting process and reduce the level of triggering antibodies, and Ig therapy may play a role when these some of these treatments are unavailable or unsuccessful in achieving a response. Requests can continue to be made for acute attacks as required. The formal access criteria proposed for this condition require that either a haematologist or a clinical immunologist makes the diagnosis and manages the treatment. This is because CAPS is a very rare condition, and is usually treated by these specialists.  |
| **Impact on demand** | There is not expected to be any impact on demand as a result of these changes.  |
|  | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | The Specialist Working Group estimated magnitude of effect:No impact against projected demand |
| **Patient number** | **13** | **17** | **24** | **19** | **13** |
| **Total Grams issued** | **3,542** | **2,684** | **4,493** | **3,216** | **1,705** |
| **% Total Grams issued** | **0.11%** | **0.07%** | **0.11%** | **0.07%** | **0.03%** |
| **Specialist Working Group knowledge development opportunities and recommendations** |
| None identified at this stage |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Eighteen months following implementation of BloodSTAR v3.0** |