

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	
<p>PROPOSED APPROACH:</p> <p>To retain Catastrophic anti-phospholipid syndrome in <i>Exceptional circumstances only</i> with the changes as outlined.</p>	<p>SUMMARY OF RATIONALE:</p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> - 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.
<p>v2.1 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)</p> <p>v3.0 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)</p>	

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 is 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	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	Catastrophic antiphospholipid syndrome	Catastrophic anti-phospholipid syndrome	No change
Specialty	Immunology	Immunology	No change
Category	<i>Exceptional circumstances only</i>	<i>Exceptional circumstances only</i>	No change
Specific Conditions	Catastrophic antiphospholipid syndrome	Catastrophic anti-phospholipid syndrome	No change
Level of Evidence	Insufficient data (Category 4a).	Insufficient data (Category 4a)	No change
Justification for Evidence Category		<p>Given the rarity of this condition, the evidence level is unlikely to extend beyond case reports and series.</p> <p>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</p>	Justification for recommendation added.

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		demonstrates that patients treated by plasmapheresis and Ig therapy demonstrate superior clinical outcomes.	
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 is 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	New text added after consideration of the literature.

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		<p>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 is not available or is contraindicated or where there is a deterioration after plasmapheresis, 2 g/kg Ig therapy over 5 days is indicated.</p> <p>Ig therapy is not indicated for chronic recurrent thrombosis, however, Rituximab has been shown to be effective in some individuals.</p>			
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	<p>A patient will qualify for IVIg when all the following criteria are met:</p> <p>Evidence of rapidly evolving thrombosis involving two or more organs</p> <p>Unequivocal laboratory evidence of</p>	<ul style="list-style-type: none"> Rapidly evolving thrombosis involving three or more organs within seven days <p>AND</p> <ul style="list-style-type: none"> Laboratory evidence of antiphospholipid antibodies (at least one of anti-cardiolipin, beta 2 glycoprotein I antibody or lupus 			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.

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	<p>antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or beta 2 glycoprotein I antibodies) Other causes of thrombotic microangiopathy are considered less likely.</p> <p>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.</p>	<p>anticoagulant)</p> <p>AND</p> <ul style="list-style-type: none"> Inadequate response to steroid therapy and plasmapheresis or a clinical deterioration post plasmapheresis <p>OR</p> <ul style="list-style-type: none"> Plasmapheresis is unavailable <p>OR</p> <ul style="list-style-type: none"> Plasmapheresis is contraindicated 	
Review Criteria		<p>Review is not mandated for this condition.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> Survival 	<p>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.</p> <p>The Specialist Working Group discussion noted the importance of gathering data on rare conditions to inform the future review of <i>the Criteria</i> 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.</p>
Dose	Confirmation by histopathology of thrombotic small vessel occlusion in at	Induction Dose – 2 g/kg over 5 days	Dosing is unchanged and advice is provided regarding when re-treatment is indicated. .

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	<p>least one organ or tissue is desirable but should not delay IVIg therapy if indicated.</p> <p>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.</p> <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>Retreatment may be required in early relapse or occurrence of a second episode.</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 style="text-align: center;">References</p> <p style="text-align: center;">(most recent update: April 2016)</p>			
<p>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. <i>Lupus</i>, 12:530–34. https://www.ncbi.nlm.nih.gov/pubmed/12892393</p> <p>Asherson RA, Espinosa G, Cervera R, Font J and Reverter JC (2002) Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment. <i>Journal of Clinical Rheumatology</i>, 8(3):157–65. https://www.ncbi.nlm.nih.gov/pubmed/17041346</p> <p>Berman H, Rodriguez-Pinto I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al (2013) Rituximab use in catastrophic antiphospholipid syndrome:</p>			

Descriptive analysis of the CAPS registry patients receiving rituximab. *Autoimmunity Reviews*, 12:1085-1090.

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https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.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

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Eighteen months following implementation of BloodSTAR v3.0