

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

v2.1 CONDITION NAME: Susac syndrome	
<p>PROPOSED APPROACH:</p> <p>To retain Susac 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"> - This is a rare autoimmune endotheliopathy where IVIg should always be given concurrently with steroids (unless the patient is actively septic or where steroids are contraindicated). - While there are no RCTs or prospective studies, this condition has a natural history of poor clinical outcome and a clear response to immunosuppressive therapy, including IVIg (as first line therapy with steroids) has been demonstrated in case series Fox (2006), Mateen (2012) and Vodopivec (2016). - National Ig usage is stable and low - in line with the expected prevalence of the condition. - Improved cost effectiveness will be attained by the revised criteria which include compliance with formal diagnostic criteria, ongoing assessment of disability, demonstration of a clinical response after four months and consideration of a trial of weaning after twelve months' treatment. - The criteria have been reviewed and endorsed by an external expert. - While this condition is not listed in either the UK (UK Department of Health, 2011) or Canadian (Ontario Regional Blood Coordinating Network, 2016) guidelines, it is noted that very rare immune-mediated disorders with evidence of immunoglobulin efficacy are not necessarily listed in guidelines but may still be approved for funded use in those countries.
<p>v2.1 CONDITION CATEGORY: Condition for which Ig uses is in Exceptional circumstances only (Chapter 7)</p> <p>v3.0 CONDITION CATEGORY: Condition for which Ig uses is in Exceptional circumstances only (Chapter 7)</p>	
<p>Role of Ig therapy: This condition is extremely rare but being increasingly recognised worldwide, so the incidence may be more common than originally thought. Given that the condition may be unrecognised or misdiagnosed, determination of the prevalence has been difficult. The condition can be self-limited but early, aggressive and sustained treatment is needed while the disease is active to avoid or minimise potential irreversible neurological damage or hearing or vision loss. Two mainstays of treatment have been intravenous corticosteroids and IVIg, however, a recent case series has suggested equal or possibly greater efficacy from plasma exchange compared to IVIg. Plasmapheresis should be considered where available. Most patients in Australia would also be treated with Rituximab but other immunosuppressant therapy including mycophenolate, azathioprine, cyclophosphamide and anti-TNF therapies have been proven to be effective (Mateen, 2012 and Vodopivec, 2016).</p>	

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	Susac Syndrome	Susac Syndrome	No change
Specialty	Neurology	Neurology	No change
Category	<i>Exceptional circumstances only</i>	<i>Exceptional circumstances only</i>	No change
Specific Conditions			No change
Level of Evidence	Insufficient data (Category 4a)	Insufficient data (Category 4a)	No change
Justification for Evidence Category		There are no RCTs nor prospective series in Susac Syndrome. However, there is a very poor natural history and a clear response to multi-agent immunosuppressive therapy including IVIg in case series (Mateen, 2012). A recent series has suggested equal or possibly greater efficacy from plasma exchange over IVIg, and plasma exchange should be considered where available (Vodopivec, 2016).	A summary of the findings has been added after consultation of the literature.
Indications		Probable or definite Susac syndrome in concurrence with high dose corticosteroids	The indication is based on Specialist Working Group consensus and consultation of the literature.

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Description and Diagnostic Criteria	Susac syndrome is a rare, microangiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Case reports show benefit of intravenous immunoglobulin (IVIg) therapy in combination with corticosteroids, with or without other immunosuppressive agents	Susac syndrome is a rare, microangiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Case reports show benefit of IVIg or plasma exchange in combination with corticosteroids, generally with, or in mild cases without, other immunosuppressive agents.			A reference to the effectiveness of plasma exchange has been included.
Diagnosis is required		Yes	By which specialty	Neurologist Immunologist Rheumatologist Ophthalmologist	This condition must now be diagnosed by a specialist in neurology, immunology, rheumatology or ophthalmology as this condition is rare and usually managed by these specialists.
Diagnosis must be verified		No	By which specialty		
Exclusion					No change

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Criteria			
Qualifying Criteria		<ul style="list-style-type: none"> • Probable or definite diagnosis of Susac syndrome has been made by the presence of at least two of the following <ul style="list-style-type: none"> - Encephalopathy with typical MRI brain changes including corpus callosum lesions or characteristic diffusion weighted imaging (DWI) hyperintense lesions - New sensori-neural hearing loss or tinnitus - Branch retinal artery occlusions (BRAOs) or ischaemia or arterial wall hyperfluorescence (AWH) on fluorescein angiography <p>AND</p> <ul style="list-style-type: none"> • Steroid therapy is being given concurrently <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Steroid therapy is absolutely contraindicated <p>AND</p> <ul style="list-style-type: none"> • A baseline assessment of disability is conducted as measured by the Modified Rankin Score 	<p>The Specialist Working Group recognised that most patients are treated with rituximab. The qualifying criteria have been reviewed by an external expert and agreed by Specialist Working Group consensus.</p> <p>The Specialist Working Group has noted that the main reason not to give steroids would be if the patient is actively septic.</p> <p>An assessment of the level of disability is made for comparison to assess the response following Ig treatment at initial review.</p>
Review Criteria		<p>IVIg should be used for four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.</p> <p>Review by a Neurologist, Clinical Immunologist Rheumatologist or Ophthalmologist is required within 4 months of treatment to determine whether</p>	<p>Review criteria and review periods have been defined with an initial measurable clinical response being required after four months' treatment for Ig</p>

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		<p>the patient has responded, and annually thereafter.</p> <p>For stable patients on maintenance treatment, review by a Neurologist, Clinical Immunologist, Ophthalmologist or Rheumatologist is required at least annually.</p> <p>Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.</p> <p>On review of the initial authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Improvement in or stabilisation of the severity of symptoms <p>AND</p> <ul style="list-style-type: none"> • Improvement in or stabilisation of disability as measured by the Modified Rankin Score compared to the qualifying assessment <p>On review of a continuing authorisation period</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> • Improvement in or stabilisation of symptoms compared to the previous review assessment <p>AND</p> <ul style="list-style-type: none"> • Stabilisation or improvement in disability as measured by the Modified Rankin Score compared to the previous review assessment <p>AND</p> <ul style="list-style-type: none"> • A trial off Ig therapy is planned once the patient is stable, unless a valid reason is provided as to why a trial is not planned or is contraindicated at this time. <p>A trial off IVIg should be attempted after a year of therapy, unless there is a contraindication to doing so, or the patient has previously relapsed after an</p>	<p>therapy to continue.</p> <p>The types of responses qualifying for re-authorisation of Ig therapy will include resolution of BRAOs, stable or improved hearing or tinnitus, stable or improved cognition or conscious state and/or improved psychosis) compared to the severity of symptoms at qualifying.</p> <p>The Specialist Working Group agreed by consensus that a trial off IVIg should be attempted after a year of therapy, unless there is a contraindication to doing so, or the patient has previously relapsed after an earlier trial of withdrawal of IVIg.</p>

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		earlier trial of withdrawal of IVIg.	
Dose	<p>Dose: 1–2 g/kg/month for one year, providing documented clinical improvement.</p> <p>Dosing above 1 g/kg per day is contraindicated for some IVIg products.</p> <p>Note: Effectiveness of IVIg therapy may be difficult to determine due to the fluctuating course of disease.</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>Induction Dose – Up to 2 g/kg over 2 to 5 days</p> <p>Maintenance Dose– 0.5 -1 g/kg every 2 to 6 weeks</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>Dosing was determined by Specialist Working Group consensus and supports a range in dose and frequency as required for weaning of Ig therapy.</p>

References

(most recent update: January 2016)

Aubart-Cohen F, Klein I, Alexandra J, et al (2007) Long-term outcome in Susac syndrome. *Medicine (Baltimore)*, 86(2):93–102.

<https://www.ncbi.nlm.nih.gov/labs/articles/17435589/>

Fox R, Costello F, Judkin, A, et al (2006) Treatment of Susac syndrome with gamma globulin and corticosteroids. *Journal of the Neurological Sciences*, 25(1–2):17–22.

<https://www.ncbi.nlm.nih.gov/pubmed/17052732>

Mateen FJ1, Zubkov AY, Muralidharan R, Fugate JE, Rodriguez FJ, Winters JL, Petty GW (2012) Susac syndrome: clinical characteristics and treatment in 29 new cases. *Eur J Neurol*, 19(6):800-11.

<https://www.ncbi.nlm.nih.gov/pubmed/22221557>

Vodopivec I and Prasad S (2016) Treatment of Susac Syndrome. *Curr Treat Options Neurol*, 18(1):3.

<https://www.ncbi.nlm.nih.gov/pubmed/26715396>

POTENTIAL OPERATIONAL IMPACT

There is expected to be minimal operational impact as a result of these changes as they are anticipated to align with current clinical practice. A neurologist, immunologist, rheumatologist or ophthalmologist will be required to make the diagnosis and management treatment. There will be slightly increased data entry required (e.g. compliance with diagnostic and other criteria) compared to the previous Ig request and review processes. Review frequency is expected to align with the usual follow-up for patients. Patients will be required to be assessed at qualifying and review using a Modified Rankin Scale, however, the scale will be presented as ‘drop-down’ menu options within BloodSTAR v3.0 and will be simple to apply. A trial of weaning should be considered after twelve months and once the patient’s symptoms are stabilised, and further a request can be made if responding patients relapse after Ig therapy has ceased.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE

Description of impact on patients:

There is not anticipated to be any significant impact on patients as a result of these criteria given that the proposed changes are based on how specialists already diagnose and manage patients with Susac syndrome. The formal access criteria proposed for this condition require that a neurologist, immunologist, rheumatologist or ophthalmologist makes the diagnosis and manages the patient treatment. This is because it is very rare and it is usually managed by these specialists. Ig therapy is one of a number of treatments that may be used, and when prescribed, is given with other treatment at the same time.

For existing patients on Ig maintenance therapy, annual reviews are required to assess the effectiveness of the treatment to improve or stabilise the severity of symptoms and degree of disability. Given that patients will already require regular review by their specialist, this requirement will not place an added burden on patients. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after at least twelve months treatment and when patients are well and stable to test whether the disease is in remission. If, patients relapse after Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made.

New patients authorised to receive ongoing Ig therapy will require an initial check after the first four months of Ig treatment to confirm that Ig therapy is improving or stabilising the severity of symptoms and degree of disability. If improvement has been demonstrated after four months ongoing treatment, Ig therapy will be continued; otherwise a different treatment would be required. The ongoing arrangements for maintenance therapy are as outlined above for existing patients.

Impact on Demand

The Specialist Working Group notes that while between seven and fifteen patients have required treatment annually over the last five years, some of these patients would have been treated for over twelve months. The use is reasonably stable and appropriate for the expected prevalence of the condition. The revised criteria will ensure that use is controlled and appropriate with evidence of a clinical response requiring to be demonstrated after four months Ig

		therapy, and that symptoms continue to improve or stabilise to remain on treatment. There is not expected to be any material impact on overall 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	7	8	11	9	15	
Total Grams issued	3,359	4,294	4,973	4,884	9,294	
% Total Grams issued	0.1%	0.12%	0.12%	0.11%	0.19%	
Specialist Working Group knowledge development opportunities and recommendations relevant to the transition to v3.0						
None identified at this stage						

END OF PUBLIC CONSULTATION DOCUMENT
Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation