2017 (v3.0) proposed changes to v2.1 of the Criteria for the Clinical use of Intravenous Immunoglobulin in Australia

v2.1 CONDITION NAME : **Autoimmune neutropenia**	
v3.0 CONDITION NAME: Autoimmune neutropenia	

PROPOSED APPROACH:	SUMMARY OF RATIONALE:
To retain Autoimmune neutropenia as a condition in *Exceptional circumstances* only with the changes as outlined.	The recommended changes are supported by factors including that: - Ig therapy is not used as first line treatment in this rare condition and will be limited to patients with severe or recurrent infections that have not responded to first and second line treatments. - The opportunity to correct the neutrophil cell count, even if only for a short period, remains an important therapeutic option in these critically ill (usually adult) patients. - The criteria will limit access to patients with severe or recurrent infection as third line treatment and will limit subsequent doses to responding patients. - Ig use is low and not expected to increase as a result of these changes - This condition is listed as a 'grey' condition in the UK NHS immunoglobulin guidelines (UK Department of Health, 2011). Indications are categorised as 'grey' if evidence is weak. The UK guidelines acknowledge that in many cases, this is because the disease is rare. Local approval is required to access IVIg for 'grey' indications. It is also listed in the national Canadian IVIg Utilisation Management guidelines (Ontario Regional Blood Coordinating Network, 2016) as recommended adjunctive therapy in urgent situations.

v2.1 CONDITION CATEGORY: Condition for which Ig is used in exceptional circumstances only (Chapter 7)

v3.0 CONDITION CATEGORY: Condition for which Ig is used in exceptional circumstances only (Chapter 7)

Role of Ig therapy: When treatment of autoimmune neutropenia is required, first line therapy is recognised to be Granulocyte-colony stimulating factor (G-CSF), followed by immunosuppression using steroids, methotrexate or cyclosporine. It is noted that steroids would not be used in children, however, they would usually respond to G-CSF. In the presence of severe or recurrent infection, Ig therapy can be an important option to treat the severe underlying infection without further immunosuppression. While it is recognised that the response is usually short lived, it provides an opportunity to improve the neutrophil count to fight the infection in these rare instances, occurring more commonly in adults than children.

The potential mechanism of action is the temporary blocking of macrophage receptors, the anti-idiotype suppression of autoantibodies and immune modulation of T and B cell function (Shastri & Logue, 1993 and Capsoni et al, 2005).

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
Condition Name	**Autoimmune neutropenia**	**Autoimmune neutropenia**	Unchanged
Specialty	Haematology	Haematology	Unchanged
Category	*Exceptional circumstances only*	*Exceptional circumstances only*	Unchanged
Specific Conditions		Autoimmune neutropenia	Specific condition must be defined
Level of Evidence	Insufficient data (Category 4a)	Insufficient data (Category 4a)	Unchanged
Justification for Evidence Category		First line treatment of Autoimmune neutropenia is G-CSF and antibiotics to treat any infection. In patients with severe infection, there are multiple small case reports and case series supporting the use of Ig therapy (Bux et al, 1991 and Bux et al, 1998 and Getta et al, 2015). Corticosteroids, cytotoxic and immunosuppressant medication and rarely, splenectomy have also been described. (Shastri & Logue, 1993 and Capsoni et al, 2005 and Bux et al, 1998). Although some long lasting responses have occasionally been reported following Ig therapy, the overall response is generally short lived and providing an opportunity to treat severe underlying infection.	This section has been drafted in line with the literature
Indications		**Severe autoimmune neutropenia unresponsive to treatment with G-CSF** **Relapse of severe autoimmune neutropenia in a patient**	Two indications have been developed in order to limit any subsequent treatment to responding patients only.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA			SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
		demonstrated to have previously responded to Ig therapy			
Description and Diagnostic Criteria	Autoimmune neutropenia is a rare disorder caused by peripheral destruction of antibody-sensitised neutrophils by cells of the reticuloendothelial system. Intravenous immunoglobulin (IVIgIVIg) may be considered among treatment options in rare circumstances when the standard treatment of G-CSF fails.	Autoimmune neutropenia is a rare disorder caused by peripheral destruction of autoantibody-sensitised neutrophils by the reticuloendothelial system. While autoantibodies to neutrophil surface antigens may be present they are not specific and do not need to be demonstrated.			Amended to recognise that the autoantibodies are difficult to demonstrate.
Diagnosis is required		Yes	By which specialty	Haematologist	The diagnosis of this rare condition will be limited to haematologists due to the rarity of the condition and requirement for bone marrow biopsy.
Diagnosis must be verified		No	By which specialty		
Exclusion Criteria					
Qualifying Criteria		**Severe autoimmune neutropenia unresponsive to treatment with G-CSF** • Persistent severe autoimmune neutropenia with a neutrophil count less than 0.5 x10^9 /L AND • Recurrent or severe bacterial infection(s) in last 6			The qualifying criteria have been developed in accordance with the literature and Specialist Working Group consensus decision making.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
		months AND • Failure to respond to G-CSF treatment AND • Non responsive to other immunosuppressant therapy OR • Immunosuppressant therapy is contraindicated **Relapse of severe autoimmune neutropenia in a patient demonstrated to have previously responded to Ig therapy** • Persistent severe autoimmune neutropenia AND • Recurrent or severe bacterial infection(s) in last 6 months; AND • Previous response following four weeks of Ig therapy demonstrated by improvement in neutrophil count (>0.5x10 9/L) or a reduction in infections	Further Ig therapy will be limited to patients in whom a clinical response was demonstrated.
Review Criteria		**Severe autoimmune neutropenia unresponsive to treatment with G-CSF** Review is not mandated for this condition. Clinical effectiveness of Ig therapy can be demonstrated by: • Improvement in neutrophil count compared to the qualifying assessment	Review periods have been considered in line with the literature. The initial treatment period is defined as four weeks. As this is short term treatment not requiring formal review for re-qualification, therefore clinical outcome data have been developed rather than review criteria.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
		• Reduction in ongoing infections compared to the qualifying assessment **Relapse of severe autoimmune neutropenia in a patient demonstrated to have previously responded to Ig therapy** Review is not mandated for this condition. Clinical effectiveness of Ig therapy can be demonstrated by: • Improvement in neutrophil count compared to the qualifying assessment • Reduction in ongoing infections compared to the qualifying assessment	
Dose	**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.**	**Severe autoimmune neutropenia unresponsive to treatment with G-CSF** **Dose: Up to 2 g/kg in a single or divided dose, weekly for 4 weeks** 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. **Relapse of severe autoimmune neutropenia in a patient demonstrated to have previously responded to Ig therapy**	Dosing has been defined in line with the literature and by Specialist Working Group consensus.

ITEM	CRITERIA v2.1	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS
		Dose: Up to 2 g/kg in a single or divided dose weekly for 4 weeks 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.**	

<table>
<tr><td colspan="4" align="center">References

(most recent update: August 2016)</td></tr>
</table>

Anderson D, Ali K, Blanchette V, et al (2007) Guidelines on the use of intravenous immune globulin for hematologic conditions. *Transfusion Medicine Reviews*, 21(2):S9–56.

https://www.ncbi.nlm.nih.gov/pubmed/17397769

Bux J, Behrens G, Jaeger G at al, (1998) Diagnosis and course of anutoimmune neutropenia in infancy: analysis of 240 cases. *Blood*,91(1):181-86.

https://www.ncbi.nlm.nih.gov/pubmed/17397769

Bux J, Kissel K, Nowak K, Spengel U and Mueller-Eckhardt C (1991) Autoimmune neutropenia: clinical and laboratory studies in 143 patients. *Annals of Hematology*, 63:249-52.

https://www.ncbi.nlm.nih.gov/pubmed/1958748

Capsoni F, Sarzi-Puttini P, Zanella A (2005) Primary and secondary neutropenia. *Arthritis Research & Therapy*, 7 (5):208-14.

https://arthritis-research.biomedcentral.com/articles/10.1186/ar1803

Getta B, Ponniah G and Ling S (2015) Intravenous immunoglobulin induces short-term reversal of drug-induced autoimmune neutropenia. *Transfusion*

Medicine, 25:347-8.

https://www.ncbi.nlm.nih.gov/pubmed/26192766

Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIGIVIG) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIgIVIg-utilization-management-guidelines-2/.

Shastri KA and Logue GL (1993) Autoimmune neutropenia. *Blood*, 81(8):1984-95.

https://www.ncbi.nlm.nih.gov/pubmed/8471760

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.pdf

UK 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

POTENTIAL OPERATIONAL IMPACT
There is not expected to be any significant operational impact as a result of this change. The revised criteria provide significantly greater guidance for access to Ig therapy and patient management than currently. There will be increased data entry required (e.g. compliance with the international consensus diagnostic criteria) compared to the previous Ig request process. These changes will form part of the communication strategy regarding the release of BloodSTAR v3.0.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE						
Description of impact on patients:	Ig therapy is not first line treatment for patients with this condition, however, it is recognised that there may be occasional circumstances when it may be useful as an option although the response is understood to be short lived. The formal access criteria now proposed for this condition require that a haematologist makes the diagnosis and manages the ongoing treatment, which is in line with current clinical practice. This is because it is a very rare condition and it is important to ensure its correct diagnosis and treatment. Most patients will respond to Ig therapy, and, if symptoms return after treatment, a further request for Ig therapy can be made. Given that treatment is for periods of up to four weeks, transition planning will ensure that any existing patients will be able to continue treatment for that timeframe during implementation. Long term Ig therapy is not required to manage this condition and therefore is no longer supported. If any patients are identified as receiving long term Ig treatment at the time of transition planning, a communication and transition strategy will be developed to ensure that the doctor has an appropriate and safe plan to manage these patients ahead of implementation of v3.0..					
Impact on demand:	Ig usage is noted to be low and reasonably stable for this rare condition. Demand is not expected to be affected as a result of these criteria, as they are expected to be in line with current clinical practice.					
	2011-12	**2012-13**	**2013-14**	**2014-15**	**2015-16**	Estimated number of patients that will be affected. The Specialist Working Group estimated magnitude of effect: No impact against projected demand
Patient number	13	13	10	12	6	
Total Grams issued	3,525	2,857	3,765	2,943	2,168	
% Total Grams issued	0.11%	0.08%	0.09%	0.07%	0.04%	

Specialist Working Group knowledge development opportunities and recommendations
None identified at this stage.

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation