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 (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis**	**Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis**	
Specialty	Immunology	Rheumatology, Immunology	
Chapter	6	6	
Specific Conditions		• Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis • ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome) • Granulomatosis with polyangiitis (Wegener Granulomatosis) • Microscopic polyangiitis	The names of the 4 clinical syndromes within ANCA have been reviewed and revised where updated names are in use. (A)
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a).	
Justification for Evidence Category	The Biotext (2004) review found one randomised trial of 34 patients and one case series of 7 patients with ANCA-associated systemic vasculitis (AASV). Different AASVs were represented in the studies. The Biotext (2004) review concluded that there is possible benefit in the treatment of AASV with IVIg if disease activity persists after standard	The Biotext (2004) review found one randomised trial of 34 patients and one case series of 7 patients with ANCA-associated systemic vasculitis (AASV). Different AASVs were represented in the studies. The Biotext (2004) review concluded that there is possible benefit in the treatment of AASV with IVIg if	Reviewed and unchanged.

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	therapy.	disease activity persists after standard therapy.	
Description and Diagnostic Criteria	ANCA associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Wegener granulomatosis; 2. microscopic polyangiitis; 3. Churg–Strauss syndrome; and 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens PR3 and MPO. ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis. Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common. IVIg has a limited role as one of several therapeutic options in relapsing disease.	ANCA associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Granulomatosis with polyangiitis (Wegener Granulomatosis); 2. Microscopic polyangiitis; 3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome); 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens PR3 and MPO. ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis. Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common. IVIg has a limited role as one of several therapeutic options in relapsing disease	Diagnostic criteria have clinical syndrome names revised.
Diagnosis is required		Yes / Which / Rheumatologist	Treating specialists have been definded (A)

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			Speciality	Immunologist	
Diagnosis must be verified		No	Which Specialty		
Exclusion Criteria	Initial therapy	First line or initial treatment for ANCA			Wording revised (A)
Indication for use	Control of vasculitic activity in rare cases of ANCA-positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression.	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy**			Two indications have been used. All qualifying patients will only receive 6 months treatment. A second indication supports the further treatment of responders who relapse following cessation of Ig therapy. Different qualifying and review criteria will apply. (A)
Qualifying Criteria	MPO or PR3 ANCA-positive systemic necrotising vasculitis with both of the following: 1. Current (or within the previous six months) standard cytotoxic immunosuppressive ANCA-vasculitis regimens; AND 2. Persistent active disease.	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** Evidence of active MPO or PR3 positive vasculitis confirmed by serology and an ANCA level above the normal reference range unless negative ANCA level with active vasculitis AND At least two reactive indicators when assessed by Birmingham Vasculitis Activity Score (BVAS) version 3 (v3) (score > 5), Erythrocyte Sedimentation Rate (ESR) (score >5) and C-reactive protein (CRP) (score >6). AND			Qualifying criteria have been defined to expand diagnostic requirements and gather data to be used as a comparison (to ensure response to Ig) should patients relapse and require further treatment in the future. (A)

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		Persistent disease despite standard Corticosteroid therapy for 6 months **u**nless steroid therapy is contraindicated AND A trial of Rituximab has failed to demonstrate a response unless Rituximab is inaccessible or contraindicated AND At least two other immunosuppressant agents have been trialled in addition to steroids and Rituximab unless immunosuppressant medication is contraindicated **Note:** The initial authorisation period is six months only. The reporting of clinical outcome data after six months treatment is strongly encouraged as a demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future. **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** Patient has previously demonstrated a clinical response following six months Ig therapy as measured by a reduction in at least one of	Requirements consistent with the original criteria have been used and revised to include rituximab treatment (if available) and steroid treatment. The Immunosuppressant therapy options are : • Cyclophosphamide • Azathioprine • Mycophenolate • Methotrexate Script added to explain the treatment being authorised.

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		Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) or ANCA level or Birmingham Vascular Activity Score (BVAS) version 3 (v3) compared to the original qualifying value. AND A description of the patient's previous response to therapy is provided AND The patient has evidence of active vasculitis as assessed by increased reactivity in at least one of ESR, CRP, ANCA or BVAS compared to level after Ig therapy. AND A description of the relapse and active vasculitis requiring treatment is provided	
Review Criteria	• Six-month review assessing evidence of clinical benefit. • Reduction in the Birmingham vasculitis activity score of more than 50% after three months. • Erythrocyte sedimentation rate and C-	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** Six-months treatment is authorised for patients in the first instance, and no review is required. The reporting of clinical outcome data is encouraged as demonstrated clinical response to Ig therapy is required for eligibility for further	Only 6 months treatment is approved initially for all patients. If patients relapse within 6 months from cessation, re-entry is supported with eligibility criteria requiring demonstration of previous response to Ig treatment and measurable relapse. Outcome data has been defined for patients on the first 6 months of treatment and encouragement given for recording the data in

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	reactive protein concentration. • ANCA titre.	authorisation, should the patient relapse in the future. **Outcome measures** Evidence of clinical benefit and response to treatment is assessed by a reduction in at least one indicator of: • Erythrocyte Sedimentation Rate (ESR) • C-reactive protein (CRP) level • ANCA Level or Birmingham Vasculitis Activity Score (BVAS) (<50% **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** Six monthly review by rheumatologist or clinical immunologist is required to assess evidence of clinical benefit. Once the patient has been in clinical remission for two years after relapse, cessation of Ig therapy should be considered **On review of an initial authorisation period** Patients demonstrate evidence of clinical benefit and response to treatment as assessed by reduction in at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score compared to the original qualifying value.	case patients should relapse. Once patients do relapse, they are eligible for maintenance therapy provided they have demonstrated a response to the first treatment. (A) Review criteria have been defined and a further trial may be indicated once patients are stable for 2 years. (A) Patients that have then demonstrated relapse, formally responded and then stabilized, will remain on treatment with an annual review. (A)

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		On review of a continuing authorisation period Once the patient has been in clinical remission for two years, a trial off therapy should be considered. Patients demonstrate evidence of clinical benefit and response to Ig treatment as assessed by stabilisation of at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score compared to the previous review score AND A trial off Ig therapy is planned unless a valid reason is provided.	
Dose	2 g/kg in single or divided doses. **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**	**Induction Dose** - 2 g/kg in divided doses **Maintenance** 0.4-1g/Kg 4 to 6 weekly **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.**	Dosing script has been modified given that induction doses of 2g/Kg should not be given as a single dose. (A) Maintenance dose has also been defined. There was insufficient evidence to justify dosing at up to 2g/Kg continuously and maintenance dosing of 0.4g to 1g/Kg was seen to be sufficient. (B)

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	outcome for each patient.		

POTENTIAL OPERATIONAL IMPACT
No operational impact is anticipated from transitioning to the revised Criteria other than it will be important that patients receive appropriate advice and information regarding the treatment period of 6 months and approach to be used in the case of relapse.

POTENTIAL IMPACT ON DEMAND			
Patient Numbers **2013-14**		The introduction of maintenance dosing and mandatory trialling off treatment after 6 months may reduce usage however is unlikely to have any significant impact on demand given the very low number of patients being treated.	

POTENTIAL IMPACT ON COST			
Current cost		**Anticipated reduction in cost, if any** **Marginal** = borderline or unchanged from current cost **Minor** = decrease by $500K - $1.99M from current cost **Major** = decrease $2M+ from current cost	**Marginal**

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