Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)] - positive systemic necrotising vasculitis

Condition for which IVIg use is in exceptional circumstances only

Specific Conditions	• Anti-neutrophil cytoplasmic antibody (ANCA) (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome) • Granulomatosis with polyangiitis (Wegener Granulomatosis) • Microscopic polyangiitis
Indication for IVIg Use	• Anti-neutrophil cytoplasmic antibody (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
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Anti-neutrophil cytoplasmic antibody (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 Proteinase 3 (PR3) and Myeloperoxidase (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.
Justification for Evidence Category	The Biotext (2004) review found one randomised trial of 34 patients and one case series of seven 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 therapy. However, in recent years, there have been a number of randomised controlled trials demonstrating the effectiveness of immunosuppressants and biologicals in achieving remission and treating relapsing and refractory disease. In particular, Rituximab is now considered a mainstay of treatment, and is now available on the Australian Pharmaceutical Benefits Schedule (PBS). The publication of the evidence based British Guidelines in 2014 for treatment of ANCA in adults, do not mention Ig therapy. It is recognized that Rituximab is more effective than Cyclosporine in refractory disease and if the patient has not had previous treatment with Rituximab, then it is the first choice. Ig therapy is only indicated in patients who have failed to respond to increased doses of immunosuppressants and a further trial of Rituximab, or in those in whom these therapies are contraindicated.
Diagnosis Requirements	A diagnosis must be made by an Immunologist, Nephrologist or a Rheumatologist.

Qualifying Criteria for IVIg Therapy

Anti-neutrophil cytoplasmic antibody (ANCA) positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression

This indication should be used for new patients and those that have never received Ig therapy for this indication. For responding patients who have relapsed after previous Ig therapy please use the indication **Relapse in Anti-neutrophil cytoplasmic antibody (ANCA) positive systemic necrotising vasculitis resistant following response to Ig therapy.**

- Active MPO or PR3 positive vasculitis confirmed by serology and an ANCA–test result above the normal reference range

AND

- Persistent active disease as assessed by at least two reactive indicators of: Birmingham vasculitis activity score (BVAS) version 3 (v3), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

AND

- Persistent disease despite standard corticosteroid therapy for at least six months

  OR

- Corticosteroid therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity

AND

- No response at least three months after a trial of treatment with Rituximab

  OR

- Rituximab is contraindicated

AND

- At least two other immunosuppressant agents have been trialled in addition to corticosteroids and Rituximab

  OR

- Immunosuppressant medication is contraindicated or has resulted in unacceptable side effects or significant toxicity

Six months treatment is authorised for patients in the first instance. While review is not mandated for this condition, reporting of clinical outcome data is strongly encouraged as 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 This indication should be used for responding anti-neutrophil cytoplasmic antibody (ANCA) positive systemic necrotising vasculitis patients who have relapsed following previous treatment with Ig therapy. For new patients and those that have never received Ig therapy, please use the indication **ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression.** • Clinical improvement in response to six months of Ig treatment was demonstrated **previously** as measured by a reduction in at least one of ESR, CRP or ANCA level or BVAS version 3 (v3) or another indicator of active disease compared to pre-treatment levels AND • Current evidence of a relapse of active necrotising vasculitis as measured by reactivity in at least one of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ANCA level, Birmingham vascular activity score (BVAS) Version 3 (v3) or another indicator of active disease AND • Unresponsive to previous Rituximab therapy OR • Rituximab is contraindicated AND • At least two other immunosuppressant agents have been trialled in addition to corticosteroids and Rituximab OR • Immunosuppressant medication is contraindicated or has resulted in unacceptable side effects or significant toxicity Six monthly review by a rheumatologist, immunologist or nephrologist 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.
Exclusion Criteria	First-line or initial treatment for ANCA

Review Criteria for Assessing the Effectiveness of IVIg Use

Anti-neutrophil cytoplasmic antibody (ANCA) positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression

Six months treatment is authorised for patients in the first instance. While review is not mandated for this condition, reporting of clinical outcome data is strongly encouraged as demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future.

Clinical effectiveness of Ig therapy may be assessed by:

- Reduction in at least one indicator of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, ANCA Level or Birmingham vasculitis activity score (BVAS) reduced by 50 percent or more, or other indicator of active disease compared to the qualifying value

Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy

Six monthly review by a rheumatologist, immunologist or nephrologist 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.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Reduction in at least one indicator of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham vasculitis activity score (BVAS) or other indicator of active disease compared to the qualifying value for this indication

  AND

- Improvement in clinical symptoms in response to Ig treatment

On review of a continuing authorisation period

- Stabilisation of at least one indicator of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham vasculitis activity score (BVAS) or other indicator of active disease compared to the previous review score

AND

- Improvement or stabilisation in clinical symptoms compared to previous review

AND

- A trial of Ig weaning towards cessation of Ig therapy is planned following two years in remission or a reason is provided as to why a trial is not planned

Dose	
	Anti-neutrophil cytoplasmic antibody (ANCA) positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression • **Induction Dose** - 2 g/kg in 2 to 5 divided doses • **Maintenance Dose** - 0.4-1g/Kg 4 to 6 weekly. 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 in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy • **Induction Dose** - 2 g/kg in divided doses • **Maintenance Dose** - 0.4-1g/Kg 4 to 6 weekly. 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.

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