ANCA serology in the diagnosis and management of ANCA-associated renal vasculitis

Date written: June 2007
Final submission: October 2007
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GUIDELINES

a. Serum anti-neutrophil cytoplasmic antibody (ANCA) measurement should not be used alone in the initial diagnosis of ANCA-associated vasculitis (AAV) but should be used in combination with the gold standard of tissue diagnosis. (Level 1 evidence)

b. Measurement of ANCA by both ELISA and indirect immunofluorescence (IIF) in combination ensures optimal test sensitivity and specificity. (Level I evidence)

c. The use of serial ANCA monitoring alone is insufficient to predict relapse or monitor disease activity. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

• Test performance increases with increasing clinical features of disease. Test performance is poor as a screening test in patients with few clinical features of AAV.

• Rapid ELISA test may be helpful as an adjunct to urgent therapeutic decisions when formal histological diagnosis is delayed, but should not supplant the need for histological confirmation of disease and ANCA IIF testing.

• Serial ANCA testing (ELISA and IIF) to monitor disease activity may be useful in some situations as:
  – disappearance of ANCA associated with disease remission and a lower risk of relapse1,2 (Level IV evidence),
  – reappearance or rising ANCA titre is of greater relevance in the setting of worsening clinical features, and
  – the persistence of anti-proteinase 3 (ant-PR3) antibodies is associated with a higher risk of relapse3 (Level IV evidence).

BACKGROUND

The primary systemic vasculitides are a group of heterogeneous clinical syndromes that are idiopathic in nature and classified by variable degrees of inflammation of the vessel wall. Classification of systemic vasculitis is complicated, although the most widely accepted of these has usually included consideration of the size of the vessel predominantly involved and the histological appearance on biopsy.

Renal involvement is particularly common in vasculitides of the small vessels; those with paucity or absence of immune deposits (namely Wegener’s granulomatosis [WG], microscopic polyangiitis [MPA] and Churg-Strauss syndrome [CSS]) are strongly associated with the presence of anti-neutrophil associated antibodies (ANCA). The utility of diagnostic classifications of these diseases, commonly referred to as the ANCA-associated vasculitides has been contentious, largely due to the lack of incorporation of histological, clinical and serological findings in the two main published classifications. In 1990, the American College of Rheumatology published classification criteria for vasculitis,4 which demonstrated high sensitivity and specificity for diagnosis of WG and CSS,5,6 but did not include AAV or MPA and was based on the presence of clinical symptoms and histopathological findings. In 1994, the Chapel Hill Consensus statement (CHCS)7 produced histological definitions for vasculitides that were not intended as classification criteria. Anti-neutrophil cytoplasmic antibodies were not included in the definitions, although the authors recognised the importance of ANCA in small vessel vasculitis, as well as the use of surrogate clinical markers of disease in the diagnosis.

A number of studies have demonstrated marked discordance of the two major diagnostic criteria, while others have proposed modifications that attempt to better incorporate histology, surrogate markers and serology8 that have been evaluated for validity with additional modifications recommended9. More recently, a four-step algorithm has been developed10 as a basis for epidemiological studies and in an attempt to provide standardised criteria for future clinical trials. This algorithm includes the use of histology, surrogate markers and serology, and uses exclusion criteria for other features that may mimic primary vasculitides.

Incidence varies between regions11 and may also have latitudinal variation. In Australia, AAV accounts for less
than 1% of end-stage kidney disease (ESKD). With the introduction of cyclophosphamide and prednisolone in the 1970s, the long-term prognosis for those with AAV improved dramatically. Due to the relatively high incidence of disease, and the evolution of AAV into a chronic relapsing disease with a 5-year 80% survival, ANCA serology is being increasingly used as a diagnostic marker of active disease. The purpose of this guideline is to review the available clinical evidence relating to the usefulness of serial ANCA testing to diagnose disease and to predict clinical relapse.

A. ANCA serology in the diagnosis of ANCA-associated vasculitides

It was some time ago that the renal lesion of rapidly progressive glomerulonephritis in the absence of identifiable immune deposits was recognised as a distinct pathology.\(^\text{1}\) Although acknowledged to have a variable clinical presentation of systemic necrotising vasculitis or in some cases, a renal limited lesion, it was some time before the Chapel Hill consensus formally defined the clinical subgroups that comprise systemic vasculitis. In the case of the pauci-immune renal lesion, three sub-groups were described, based on clinical and histological variants:\(^\text{1}\)

1. Wegener’s granulomatosis was defined as a granulomatous inflammation affecting the respiratory tract and necrotising vasculitis affecting small-sized to medium-sized vessels, where necrotising glomerulonephritis is common.

2. Churg-Strauss syndrome was defined as an eosinophil rich granulomatous inflammation in the respiratory tract, with necrotising vasculitis affecting small-sized to medium-sized vessels and associated with asthma and eosinophilia.

3. Microscopic polyangiitis was also described as necrotising vasculitis, with few or no immune deposits, affecting small vessels. Necrotising arteritis involving small-sized and medium-sized arteries might be present, and necrotising glomerulonephritis is very common. Pulmonary capillaritis frequently arises.

The renal lesion of pauci-immune vasculitides is recognised in the early stages by diffuse necrosis of capillary loops, with progression to diffuse proliferative, pauci-immune glomerulonephritis with basement membrane rupture and cells in Bowman’s space and an associated interstitial reaction. As the disease progresses, proliferative glomerulonephritis is the end-stage of disease.

B. Neutrophil cytoplasmic antibodies

It was in 1982 that ANCA’s were first described in a cohort of patients with segmental necrotising glomerulonephritis. Davies et al. described cytoplasmic staining of neutrophils when studying nuclear antibodies using IIF in 8 patients, 7 of whom had positive Ross River virus serology.\(^\text{1}\) It was shortly after, that the association of ANCA’s with WEG\(^\text{1}\) and MPA\(^\text{1}\) was described.

ANCA’s are antibodies directed against primary granules of neutrophil and monocyte lysosomes. Without ethanol fixation, all ANCA’s stain in a cytoplasmic distribution. However, following ethanol fixation, two distinct patterns are described, cytoplasmic (cANCA) and perinuclear (pANCA), depending on their relative charge.

1. The staining of ANCA reaction with proteinase (PR3) a weaker cation or neutral protein, will result in a cytoplasmic fluorescent pattern called cANCA.

2. When cytoplasmic granules redistribute resulting in a pANCA pattern, a number of antigens have been identified, of which myeloperoxidase (MPO) is the only one of clinical importance.

ANCA antibodies (PR3 and MPO) are detected in serum using ELISA, freely available in kit format.

The international consensus statement on reporting of ANCA recognised the association with other diseases with ANCA’s that have atypical staining patterns on IIF or antigens other than the two described (PR3 and MPO) and recommended both IIF and ELISA testing when seeking to identify ANCA, but stressed the importance of histological correlation as the gold standard.\(^\text{1}\) The statement proposes screening ANCA by IIF followed by confirmation by both PR3 and MPO ELISA and myeloperoxidase-ELISA. Furthermore, it recommends that negative results by IIF should also be tested by ELISA, as 5% of samples are only identified by ELISA.

ANCA test performance

Although it was noted in the Chapel Hill statement that ANCA’s (IIF/ELISA) are useful in the definition of small vessel vasculitis with the renal lesion being that of pauci-immune focal necrotising glomerulonephritis, the presence of ANCA’s was not considered in the diagnostic schema. It has since been demonstrated that the use of the Chapel Hill criteria in isolation has poor predictive value,\(^\text{2}\) and studies have since focused on the diagnostic utility of the various ANCA markers in comparison with histological diagnosis.

Earlier studies\(^\text{3-5,12}\) demonstrated limited sensitivity of ANCA by IIF alone, often examining only one disease group. An early study incorporating ELISA assays by Sinico et al.\(^\text{6}\) examined a renal specific population of rapidly progressive renal failure and/or disease with systemic vasculitis. Prospective analysis of 1535 serum ANCA’s in 920 consecutive patients, using histology as comparator, confirmed a high sensitivity and specificity for ANCA by IIF, with higher sensitivity when used in conjunction with ELISA.

With the development of standardised techniques for IF and ELISA, collaborative groups have determined the diagnostic value of standardised ANCA assays. The largest of these is from the EC/BR project for ANCA assay standardisation,\(^\text{7}\) a multi-centre analysis of ANCA assays compared with histology, which comprised 169 prospective and 189 retrospective biopsies and sera, along with 184 disease controls and 740 healthy controls. When using ANCA IIF and ELISA in combination, the tests were of high specificity (99%), with sensitivity of 73% and 87% for WG and MPA, respectively. The conclusion is that the value of the IIF test for ANCA detection can be greatly increased by the
 addition of ELISA. The authors did note, however, that in a significant number of patients with idiopathic small vessel vasculitis, the ANCA results were negative. Similarly, Harris et al. compared the diagnostic performance of ELISA and IIF, and found the highest sensitivity with combined testing (92%) and the highest positive predictive value with combined ELISA and IIF (73%), although the equivalent negative predictive value for each test individually was 99% and 98%, respectively. In a smaller study, dual testing in a single centre study with 123 patients with either WG or MPA demonstrated ANCA positivity in 97%.25

There are only two meta-analyses of note. One examined the utility of IIF for cANCA testing alone in the diagnosis of WG, demonstrating a pooled sensitivity of 91% (95% CI, 87%, 95%) for patients with active disease and 63% for inactive disease. The other was slightly larger, examining MPO ELISA testing.26 Myeloperoxidase performance again demonstrated best sensitivity and specificity with combined testing of IIF and ELISA, 84.7% (70.7%, 98.7%) and 98.6% (97.9%, 99.3%) respectively, encompassing 5 studies that were considered robust.

It has furthermore been demonstrated that the ANCA test is best used in cases with a high index of clinical suspicion, that it is extremely useful in patients with multiple clinical symptoms of WG, where a post-test probability of ~98% was demonstrated, but less useful in patients with only one symptom of WG, in this case with a post-test probability of only 7%-16%. This underlines the problem that ANCA-associated vasculitides are very rare diseases and the ANCA test applied to the general population (for pre-test probability) results in a large number of false-positives, irrespective of high test specificity. This was further demonstrated by Mandl et al., who showed that the ordering of ANCA test in patients with a low suspicion of ANCA-associated vasculitis, reduces false-positive rates.

It has been recognised that mostly published data come from specialised research laboratories so that do not accurately reflect the performance of assays under routine clinical conditions. Russell et al. demonstrated on 615 consecutive samples that with the relatively high sensitivity of combination PR3-ANCA and MPO ELISA (72%) that significant labour and cost savings could be made by initial ELISA screening with IIF confirmation.27 Others have demonstrated the superiority of ELISA as a method for detecting ANCA28 and our recent study, in attempting to meet the clinical need for urgent ANCA testing when IIF is not available within hours, compared rapid qualitative ELISA with quantitative IIF and quantitative ELISA in 103 consecutive samples of which were positive for MPO/PR3. In this study, Aslam et al. showed a high sensitivity of 82%, specificity 97%, PPV 92%, and NPV 93%.

B. ANCA serology in the monitoring of relapse and treatment of ANCA-associated vasculitis

ANCA titres are commonly monitored serially on the grounds that a rise/fall or disappearance may correlate with the clinical course and suggest relapse or remission. Thus, it is thought that timely identification may allow early detection of disease relapse, which can subsequently be confirmed on clinical findings or further investigation and allow prompt treatment. It has also been suggested that pre-emptive treatment adjustments based on a change in ANCA titre may prevent disease relapse.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for ANCA and kidney failure were combined with MeSH terms and text words for analysis ANCA (immunology, blood, diagnostic use), CD14, ELISA, immunoglobulin and biopsy. The search was carried out in Medline (1966 - August Week 3, 2006).

Date of searches: 22 August 2006.

WHAT IS THE EVIDENCE?

Birck and co.30 performed a systemic review of the literature addressing the clinical value of serial ANCA monitoring in patients with systemic vasculitis. Small sample size (rather than 10 patients), studies where there was no association to a particular vasculitic syndrome, and studies where treatment was based on ANCA titre were excluded. From an initial 3611 citations, 22 studies of 950 patients were included. Qualitative analysis showed that only a minority of studies (4) reported consecutive patient enrolment, prospective data collection and independence of both the index and reference tests. Differences in methodology (especially the nature of the ANCA assay and the clinical definition of disease relapse) were sufficient to not allow the authors to draw a firm conclusion as to the usefulness of ANCA serial monitoring.

A number of cohort studies have been performed (often with retrospective data entry) and with differences in the ANCA assay methodology and definition of disease activity. Machsacl et al.31 tested over 7500 sera for ANCA-IIF that were referred for ANA testing. Seventeen were found positive and their medical details reviewed; 14 consecutive patients with positive ANCA and glomerulonephritis were followed up for a mean duration of 6.3 years. Eleven patients became ANCA negative during clinical remission and 5 relapses occurred with ANCA changing from negative to positive. Two patients developed a positive ANCA without clinical relapse.

Geffraud-Ricouard et al.1 studied the ANCA (IIF and ELISA) specificities of 98 patients with various types of systemic vasculitis. Serial ANACs were obtained in 44 patients – there was no association with relapse, however, disappearance of ANCA was associated with remission.

Kerr et al.32 analysed 106 patients with WG, of whom 68 had serial ANCA titres by IIF every 1–3 months. Active disease was assessed clinically as well as with biopsy confirmation if possible. A total of 23 patients had sustained remission. The 45 remaining patients had active disease.
A subset of 17 patients either in remission or with stable “smouldering” disease had disease flares, of which only 4 had a rise in cANCA titre. Out of all the patients studied, 16 patients had a four-fold rise in ANCA titre of which 7 did not have a relapse.

Gordon et al.15 studied relapse in 150 consecutive patients with systemic vasculitis – 12 with polyarteritis, 95 with microscopic polyarteritis and 43 with WG; ANCA were detected by IIF. Positivity at the time of relapse ranged from 2/5 in polyarteritis to 12/13 with WG. Specificity again was low.

Koehler and Specks13 studied 91 patients with Churg-Strauss syndrome. Serial ANCA testing was performed in 74 patients and 22/30 tested at the time of diagnosis were ANCA positive. Twelve of 16 patients tested during a 74 patients and 22/30 tested at the time of diagnosis were Strauss syndrome. Serial ANCA testing was performed in nothavearelapse.

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Renal Vasculitis

Tervaert et al. looked at 58 patients with biopsy-proven WCo. They were screened every 3 months for clinical activity and had ANCA estimation by IIF performed monthly. Twenty patients had a rise in ANCA titre: 9 patients were treated with an increase in immunosuppression and 11 were treated only if there was a clinical relapse. Nine of the latter group relapsed whereas there were no relapses in the pre-emptively treated group.

SUMMARY OF THE EVIDENCE

Attempted system review demonstrated the shortcomings of the available evidence with methodological heterogeneity precluding firm conclusions. There are differences in ANCA assays (IIF and ELISA) and in patient populations and the definition of active disease. Data has been obtained both retrospectively and prospectively (but not always consecutively).

Studies have suggested that the ELISA and particularly, capture ELISA, is more sensitive and specific, although Nowack et al. found capture ELISA no better than other laboratory parameters.

Tervaert et al. paper from 2000 suggests that pre-emptive treatment in response to a rise in ANCA titre may reduce the risk of relapse and also reduce the total immunosuppression burden. Given the lack of certainty about the association between ANCA and disease activity, this cannot currently be recommended.

Monitoring of serial ANCA titres may be of benefit in individual patients; however, with current evidence this should not lead to pre-emptive treatment but at best, careful patient observation.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1. A prospective trial with both clinical (BVAS) and if possible, histological confirmation of disease relapse, agreed treatment protocols and with ANCA testing blinded to patient status is needed. Due to the small numbers of patients, this will require multiple investigating centres and a long period of recruitment and follow-up.

2. New research focusing on the identification of novel markers of disease activity may also help in determining episodes of relapse and disease activation.

CONFLICT OF INTEREST

Grant Luxton has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

Robyn Langham has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

REFERENCES


### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Disease</th>
<th>ANCA test</th>
<th>Definition of change in titre</th>
<th>Assessment of disease activity</th>
<th>No. of patients</th>
<th>No. of relapses</th>
<th>No. of relapses with change in ANCA</th>
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<td>1990</td>
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<td>2 positive ANCA without relapse</td>
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<td>Prospective cohort</td>
<td>Systemic vasculitis</td>
<td>IF and ELISA</td>
<td>Rise in titre</td>
<td>Clinical assessment</td>
<td>98</td>
<td>44</td>
<td>1</td>
<td>No association</td>
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<td>1993</td>
<td>Prospective cohort</td>
<td>Wegener’s granulomatosis</td>
<td>IF</td>
<td>4 x rise in titre</td>
<td>Clinical and renal biopsy</td>
<td>106</td>
<td>68</td>
<td>17</td>
<td>Disappearance of ANCA was associated with remission</td>
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<td>1993</td>
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<td>Prospective cohort</td>
<td>Churg–Strauss syndrome</td>
<td>IF</td>
<td>Positivity</td>
<td>Clinical assessment</td>
<td>91</td>
<td>74</td>
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<td></td>
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<tr>
<td>Jayne et al.</td>
<td>1993</td>
<td>Prospective cohort</td>
<td>Systemic vasculitis</td>
<td>IF and ELISA</td>
<td>2 x rise to positive or a more than 30% rise in titre</td>
<td>Clinical assessment</td>
<td>60</td>
<td>23</td>
<td>19</td>
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<td>Davenport et al.</td>
<td>1995</td>
<td>Retrospective cohort</td>
<td>Wegener’s granulomatosis</td>
<td>IF</td>
<td>4 x rise in titre</td>
<td>Clinical assessment</td>
<td>37</td>
<td>32</td>
<td>19</td>
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<td>1998</td>
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<td>Clinical assessment</td>
<td>94</td>
<td></td>
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</table>

IFF, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay; FEIA, fluorescent enzyme immunoassay; BVAS, Birmingham Vasculitis Activity Score; WG, Wegener’s granulomatosis.