The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis: a literature review and meta-analysis

Authors' objectives
To review the clinical utility of antineutrophil cytoplasmic antibody (c-ANCA) as a diagnostic marker for Wegener's granulomatosis.

Searching
MEDLINE was searched from 1966 to June 1993 for studies on humans, published in the English language only. The keywords and search terms included 'antineutrophil cytoplasmic antibody', 'antineutrophil antibody', 'antibodies', 'neutrophils', 'pulmonary-renal syndrome', 'Wegener granulomatosis', 'vasculitis' and 'glomerulonephritis'. The reference lists of included articles, and the bibliographies of review articles and standard texts were handsearched for further studies. Unpublished material was not sought.

Study selection

Study designs of evaluations included in the review
Diagnostic case-control and cohort studies were eligible for inclusion. The included studies were required to define a systematic method of patient selection, e.g. consecutive patients.

Specific interventions included in the review
Studies of c-ANCA for the diagnosis of Wegener granulomatosis were eligible for inclusion. The included studies measured c-ANCA by indirect immunofluorescence. A positive c-ANCA result was defined as any positive titre.

Reference standard test against which the new test was compared
The included studies had to specify acceptable reference standard criteria for establishing the diagnosis of Wegener granulomatosis: the ear, nose, throat, lung and kidney staging system; the American College of Rheumatology criteria; the Fauci criteria. The first two of these require biopsy confirmation, while the latter is clinicopathologic (see Other Publications of Related Interest nos. 1-3).

Participants included in the review
No inclusion criteria relating to the study population were specified. Patients with suspected Wegener's granulomatosis were included.

Outcomes assessed in the review
The included studies were required to report sufficient data to construct 2x2 contingency tables. The outcome measures reported in the review were sensitivity and specificity.

How were decisions on the relevance of primary studies made?
Articles had to pass through a multi-staged assessment process with independent examination by two or three reviewers.

Assessment of study quality
Articles were scored (maximum score 13) on five areas of methodology deemed to be of importance for studies evaluating diagnostic tests: study design; data collection (prospective or retrospective-prospective); method of patient selection (random or consecutive); whether greater than 50% of controls had a diagnosis (e.g. vasculitis, pulmonary-renal syndromes, malignancy, or fungal infections) suitable for ruling out Wegener's granulomatosis; and blinding of the outcome assessment. The authors did not state how papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. 2x2 contingency tables were constructed for patients with and without Wegener's granulomatosis, versus positive and negative c-ANCA results; disagreements between reviewers were resolved by consensus.

Methods of synthesis

How were the studies combined?
The sensitivity and specificity of c-ANCA testing were calculated for Wegener's granulomatosis overall and, where applicable, for active and inactive Wegener's granulomatosis. Summary estimates of sensitivity and specificity were derived by pooling the averages weighted by the number of patients in each study. A fixed-effect model was applied for pooled estimates unless there was heterogeneity across the studies, in which case a random-effects model was applied. 95% Confidence intervals (CIs) were derived for all estimates, including the summary measures, using exact methods for proportions.

How were differences between studies investigated?
A chi-squared test of homogeneity was evaluated for the 15 studies. Analyses were repeated for studies with a quality score of greater than 7, compared with those with a quality score of less than 7.

Results of the review
Fifteen studies were included: 11 case-control (n=5,219) and 4 cohort (n=8,344).

The pooled sensitivity of c-ANCA for Wegener's granulomatosis overall was 66% (95% CI: 57, 74) and the pooled specificity was 98% (95% CI: 96, 99.5).

Four of the 15 articles gave disease activity information; in all 4 studies the sensitivity of c-ANCA was higher for patients with active disease than for those with inactive disease. For active Wegener's granulomatosis, the summary sensitivity was 91% (95% CI: 87, 95) and the summary specificity was 98.6% (95% CI: 97, 99.9). For inactive Wegener's granulomatosis, the summary sensitivity and specificity were 63% (95% CI: 57, 69) and 99.5% (95% CI: 99.1, 99.7), respectively.

The quality of the studies ranged from 4 to 10 points out of a possible 13. Only 3 studies satisfied the criteria for a highest quality study (a score of at least 10); 2 of these reported sensitivities of 39 and 46%, whilst the third reported a sensitivity of 92%. When the articles were stratified on the basis of a quality score of 7, the results were not significantly different from the overall results.

Authors' conclusions
c-ANCA test results may serve clinicians as adjunct evidence for the diagnosis of Wegener's granulomatosis, but these results must be viewed in the context of the patient's clinical picture and disease activity and the prevalence of Wegener's granulomatosis in the clinical setting in which the patient is seen. The test should be used cautiously when pursuing the diagnosis of Wegener's granulomatosis. There is little value in using a c-ANCA to screen for Wegener's granulomatosis in low-prevalence situations.

CRD commentary
The review addressed a clear research question with well-defined inclusion criteria. Details of the included primary studies and review methodology were well reported. However, the search strategy was somewhat limited, and the authors stated that no attempt was made to identify unpublished studies. It is therefore possible that relevant data may have been omitted. No assessment of publication bias was reported. The methods of data analysis were reasonable. The review may have benefited from a more comprehensive investigation of sources of heterogeneity; e.g. the use of an overall score to assess the impact of study quality may well mask effects from individual components of quality. The clear discussion highlighted the limitations of the review. The authors' conclusions follow broadly from the data presented.
Implications of the review for practice and research
Practice: The authors stated that clinicians should use c-ANCA testing cautiously when pursuing a diagnosis of Wegener's granulomatosis.

Research: Prospective studies, evaluating patients with suspected vasculitis for c-ANCA, and following them up for outcome determination, are required.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.