Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease


CRD summary
This review concluded that anti-Saccharomyces cerevisiae and perinuclear antineutrophil cytoplasmic antibodies have good specificity, but poor sensitivity, for ulcerative colitis and Crohn's disease. The authors' conclusions are supported by the results presented, but should be interpreted with some caution given the presence of substantial variation between the studies.

Authors' objectives
To assess the accuracy of anti-Saccharomyces cerevisiae (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in inflammatory bowel disease (IBD), and to assess their ability to discriminate between ulcerative colitis (UC) and Crohn's disease (CD).

Searching
MEDLINE, EMBASE, the Cochrane Library and the 'Related Articles' function in PubMed were searched up to January 2006; the search terms were reported. References of identified studies were screened for additional studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not specified in terms of the study design. The control groups in case-control studies were either patients with non-IBD conditions or healthy volunteers. It was unclear whether all studies used a diagnostic case-control design or whether diagnostic cohort studies were also included.

Specific interventions included in the review
Studies that assessed ASCA or pANCA were eligible for inclusion. The antibodies evaluated by the included studies were: ASCA immunoglobulin (Ig) G, ASCA IgA, ASCA unspecified, ANCA lactoferrin, ANCA myeloperoxidase, ANCA cathepsin, pANCA and cANCA. The manufacturers of the tests were: Prometheus laboratories, San Diego, USA; Medipan Diagnostica, Selchow, Germany; INOVA Diagnostics, San Diego, USA; Bouty, Milan, Italy; Aesku.lab Diagnostika, Wendelsheim, Germany; Euroimmun, Gross Gronau, Germany; and Scimedx, Denvill, USA.

Reference standard test against which the new test was compared
Studies that included clinical, radiological, endoscopic or histological diagnosis as the reference standard were eligible for inclusion. No details of the reference standards used in the included studies were reported.

Participants included in the review
Studies that did not include patients with a diagnosis of UC or CD were excluded. The overall age range was 1 to 94 years; some studies only included paediatric populations. Some patients were receiving immunosuppressant therapy.

Outcomes assessed in the review
Studies that provided data on sensitivity and specificity were eligible for inclusion. The outcomes reported in the review were sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio (DOR) and the area under the receiver operating characteristic curve (AUC).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the studies for relevance. In the case of studies with possible patient overlap, three reviewers discussed these and only the best quality study was included.
Assessment of study quality
The studies were assessed for methodological quality using the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. The studies were assigned a quality score based on both these tools, but it is unclear how these were calculated. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted the data; any disagreements were resolved through referral to a third reviewer. Sensitivity and specificity were either extracted directly from the studies or derived from 2x2 tables of test performance on a per patient basis. For UC, the sensitivity and specificity of pANCA in different combinations with ASCA were extracted. For CD, the sensitivity and specificity of ASCA in different combinations with pANCA were extracted.

Methods of synthesis
How were the studies combined?
The pooled sensitivity and specificity were calculated using DerSimonian and Laird random-effects models. A summary receiver operating characteristic analysis was undertaken using the Moses-Littenberg method; AUC was calculated using this model. Pooled DORs and positive and negative likelihood ratios were calculated from pooled estimates of sensitivity and specificity.

How were differences between studies investigated?
The Q statistic was used to assess heterogeneity. Subgroup analysis was carried out to assess the effects of colonic CD, a study quality score of at least 18 (STARD criteria), a study quality score of at least 11 (QUADAS tool), use of the Prometheus assay system and use of DNAase in the assay. Weighted and unweighted meta-regression using the DOR was carried out with the following covariates: gender, quality score, use of DNAase and paediatric study population.

Results of the review
Sixty studies (3,841 UC patients, 4,019 CD patients and 3,748 controls) were included.

Eighteen studies were judged to be of high quality, with STARD summary scores ranging from 3 to 14 and QUADAS summary scores ranging from 5 to 24.

Diagnosis of CD.
The most sensitive test was ASCA IgG or IgA positive antibodies in sera that were pANCA negative. This was evaluated in 8 studies (n=1,321). The sensitivity ranged from 43 to 66%; the pooled sensitivity was 55% (95% confidence interval, CI: 52, 59). The specificity for this combination ranged from 87 to 98%; the pooled specificity was 93% (95% CI: 91, 95). There was no statistical evidence of heterogeneity (p>0.1). The best pooled specificity (100%, 95% CI: 95, 100) was obtained when sera tested positive for ASCA IgG antibody and negative for pANCA. This combination was only evaluated in 2 studies (190 patients).

Diagnosis of UC.
The most sensitive test was positive pANCA with no information on ASCA status. This was evaluated in 31 studies (4,054 patients). The sensitivity ranged from 9 to 82%; the pooled sensitivity was 55% (95% CI: 53, 58). The specificity ranged from 28 to 96%; the pooled specificity was 89% (95% CI: 87, 90). There was strong evidence of heterogeneity (p<0.001). Testing for subgroups of pANCA led to decreased sensitivity with no improvement in specificity. The best pooled specificity (94%, 95% CI: 93, 96) was obtained for the combination of pANCA positive and ASCA negative; the pooled sensitivity for this test was 51% (95% CI: 48, 55). This test combination was evaluated in 14 studies (2,072 patients).

Diagnosis of IBD.
The most sensitive test for the diagnosis of IBD was the presence of pANCA or ASCA of any class. This was evaluated in 5 studies (839 patients). The pooled sensitivity was 63% (95% CI: 58, 67) and the pooled specificity 93% (95% CI: 89, 95). There was no evidence of statistical heterogeneity. The most specific test was pANCA alone, which was evaluated in 27 studies (6,117 patients). The pooled specificity was 97% (95% CI: 96, 98) and the pooled sensitivity 33% (95% CI: 31, 34). There was substantial heterogeneity in both sensitivity and specificity (p<0.001).

Subgroup analysis.

The results were generally similar for studies of paediatric populations. Test combinations for colonic CD were consistently less specific and less sensitive than for overall pooled results. This was confirmed by meta-regression, which showed a decrease in the relative DORs for studies reporting on colonic CD compared with those reporting on mixed populations. No effect of study quality on the results was found.

**Authors’ conclusions**
The specificity of ASCA and pANCA for CD and UC is good but these tests showed poor sensitivity. These antibodies may be particularly useful to differentiate CD and UC in paediatric populations.

**CRD commentary**
This review addressed a focused question which was supported by clearly defined inclusion criteria. The literature search was adequate for published data but no attempts were made to locate unpublished studies, thus the review may be subject to publication bias. Details of the review process, which included appropriate steps to minimise bias, were reported. A quality assessment was undertaken, but the results were reported as overall quality scores and it was unclear how these were calculated. In addition, the tools used were specifically designed not to incorporate quality scores. Some study details were reported in the tables but a detailed breakdown of study quality was lacking, making it difficult to determine the validity of individual studies.

The methods used to pool the studies were appropriate and pooled results for the test combinations evaluated were tabulated clearly. Overall, the authors’ conclusions are supported by the results presented, but should be interpreted with some degree of caution given the substantial heterogeneity remaining in many of the comparisons presented and, to some extent, the failure to appropriately investigate the effects of study quality.

**Implications of the review for practice and research**
Practice: The authors stated that a negative pANCA or ASCA in IBD cannot be used to rule out the disease, but high specificity means that a positive test is useful in confirming the diagnosis.

Research: The authors stated that there is a possible role for pANCA testing in paediatric populations but this needs further investigation.

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