

ANCA testing

Rational requesting or rationing testing?

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The appropriate use of antineutrophil cytoplasm antibody (ANCA) tests

The UK government has acknowledged that up to 70% of medical diagnoses now rely on pathology laboratory analyses.¹ One consequence of such reliance is an ever increasing laboratory workload, usually, in National Health Service laboratories, at a rate in excess of the financial resources to support it. It follows that this demand can only be serviced by increased efficiency.

One area where demand has risen sharply in the past decade is in the field of antineutrophil cytoplasmic antibody (ANCA) testing. Since the association of ANCA with Wegener's granulomatosis (WG) in 1985,² an increasing number of autoimmune, drug induced, and infectious disorders have been shown to have an association with ANCA.³⁻⁸ However, overall, the data suggest that these ANCA do not help to elucidate the diagnosis or prognostic features of these disorders (reviewed in Savige *et al*, 2000⁹). In addition, there is increasing evidence to suggest that ANCA may be of help, albeit limited, in categorising inflammatory bowel disease.¹⁰⁻¹¹ Low sensitivity limits the diagnostic use of ANCA in this area.¹²⁻¹³

As indicated in the consensus document,¹⁴ the principle use of ANCA testing remains as an aid to diagnosis in the necrotising vasculitides (such as WG, microscopic polyangiitis, Churg-Strauss, and pauci-immune crescentic glomerulonephritis). Untreated, these conditions have considerable morbidity and mortality.

In this issue of the *Journal of Clinical Pathology*, Sinclair *et al* have reviewed their experience over a six month period of a "gating policy", based on clinical information given to the laboratory at the time of request, which has been in place for 10 years.¹⁵ This policy directs requesting almost exclusively towards the diagnosis of the necrotising vasculitides. Their data suggest that their strategy significantly reduces ANCA requesting and they contend that this has not resulted in missed or greatly delayed diagnoses.

More usually, laboratories offer an "open door" testing service; that is, unrestricted testing of all samples arriving in the laboratory without regard to clinical background. Our own experience shows that in this scenario a large number of immunofluorescent ANCA are detected outside the context of necrotising vasculitis.¹⁶ Further retrospective studies have confirmed that open door testing has a low yield.¹⁷⁻¹⁹ In these circumstances, the positive predictive value (PPV) of the assay for the necrotising vasculitides is very low. Indeed, McLaren *et al* showed that in the context of neurological disease the PPV was 0%, at an estimated cost of £12 000 over a four year period.¹⁹ With increasing attention to context and to symptomatology the PPV can be greatly improved, being highest in those with renal disease.²⁰

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Of some concern, the present study relies very heavily on the quality of clinical data included on request forms. This has several implications for the laboratory. First, personal experience suggests that request forms are often inadequately completed, many with no clinical details included at all. These are rejected under the Sinclair rules. Second, who is the gatekeeper? A senior member of staff would need to dedicate a considerable amount of time to this additional task. We receive over 5000 ANCA requests each year. At 30 seconds to review each form this would equate to 42 hours each year, a full working week. Third, electronic requesting is increasingly available. This uses coded comments available to the clinician, including codes such as "vasculitis screen", and effectively bypasses the request form review.

Equally, in the limited format of a request form, omission of key "trigger" words, in an otherwise correctly completed form, may lead to unintentional yet unwarranted delay in the diagnostic process. Indeed, Sinclair *et al* describe one such case in their series. The patient was initially "query mixed connective tissue disease" and only later were the data of "episcleritis, haematuria, and proteinuria" made available. WG, in keeping with many autoimmune disorders, may present with a wide variety of symptoms, and musculoskeletal involvement is present in 60% of patients.²¹ In the case described, diagnostic delay was only two days, but that was because of a further request with "appropriate" symptomatology. It was felt that this had not been detrimental to the patient.

In the context of demonstrated renal involvement any delay is of concern. It has been shown that in the necrotising vasculitides the most important factor in determining outcome is the presence of renal involvement.²² The potential cost to the patient and to the service of a missed diagnosis of glomerulonephritis could be extensive, resulting for example in plasma exchange or dialysis. Locally, a course of seven exchanges would cost approximately £2500. Furthermore, mortality is increased in patients who present late. Potentially, the savings made by rejecting the 25% of samples dictated by the gating policy could be outweighed by the cost of a missed diagnosis in a single patient. One further question that remains unanswered and unanswerable by this study is how many patients with ANCA associated vasculitis remained untested and undiagnosed? One would hope the answer was extremely small, because clinical suspicion should drive further investigation, as Sinclair *et al* have been careful to point out.

The counter argument to the above concern is that the detection of ANCA is only one datum point in the diagnosis. It should be remembered that the presence of an autoantibody is neither essential (not currently included in disease definitions) nor sufficient to make a diagnosis of necrotising vasculitis.¹⁶ This being the case, it is the responsibility of the clinician to interpret any given pathology test result, not in isolation, but in the context of the patient's case history and other investigations.

SO WHAT APPEAR TO HAVE BEEN THE TRUE EFFECTS OF THE GATING POLICY?

First, it would appear to have acted as a brake on workload increases. In comparing the workload of Sinclair *et al* with our own regional reference laboratory in

Bristol, corrected for differences in the population served, they would appear to perform far fewer tests (perhaps as few as one third) for each head of the population.

Second, it is quite difficult to determine whether the gating policy per se has affected workload balance. We have no data on the workload balance in Sinclair's department before the introduction of the gating policy. In attempting to contrast the gating policy with "open door" centres we have further divergent data. The audit of Edgar *et al* showed a very high proportion of requests from patients with disorders other than necrotising vasculitis (73%) in a clinician led environment.¹⁷ In contrast, Mandl *et al* undertook a retrospective study to consider the possible outcome had they applied test ordering guidelines.¹⁸ These were similar to those used by Sinclair *et al*.¹⁵ Mandl *et al* concluded that using their guidelines would have reduced test ordering by 23%, remarkably similar to the 25% of Sinclair *et al*. Mandl and colleagues also suggested that this would improve the PPV and hence diagnostic usefulness. Unfortunately, PPV data were not available in the Sinclair study.

The third unquantifiable outcome is that the gating policy may have led to a more educated clinician base with a clear understanding of the limitations of ANCA testing, leading to self limitation of use.

It would seem then that workload has been reduced but it is still unclear as to whether this has resulted in more appropriate testing. We are left with the impression that a gating policy may work well to control workload, but the effect on clinical usefulness remains speculative. This can only be resolved

by a prospective study based on a clear audit of current workload, case mix, and predictive values in a centre using an open door strategy, followed by the introduction of a Sinclair-like rules based policy and subsequent re-audit. Any volunteers?

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