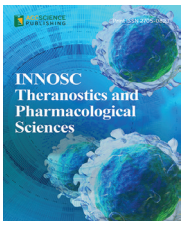
INNOSC Theranostics and Pharmacological Sciences 2022 Vol. 5 (No. 2) pp: 15-21

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INNOSC Theranostics and Pharmacological Sciences

Journal homepage: https://accscience.com/journal/ITPS



RESEARCH ARTICLE

Poor Adherence to Indications for Anti-neutrophil Cytoplasmic Antibody Testing in a South African Tertiary Hospital

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Received**:* January 26, 2023; ***Accepted: June 26, 2023; ***Published***: July 12, 2023 ***DOI:*** https://doi.org/10.36922/itps.v5i2.338

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Abstract:

Appropriate use of laboratory investigations is increasingly important in resource-constrained environments. In this study, we reviewed the anti-neutrophil cytoplasmic antibody (ANCA) testing practices in a tertiary hospital in South Africa. A retrospective file review was conducted, encompassing all ANCA tests ordered over 12 months, including both inpatients and outpatients. Sociodemographic and clinical details were extracted from the patient records. All requests were assessed against the International Consensus Statement of 1999, which provides clinical guidelines for the indications for ANCA testing. Of the 945 ANCA tests requested, 790 patient records were reviewed, while 155 records were found to be missing, and 62 patients had multiple tests. Only 193 patients (24.4%) had indications for ANCA testing that met the guidelines. The most common tests done outside guideline indications were critical limb ischemia (9.6%), stroke (7.3%), uveitis (5.7%), renal impairment (4.9%), and interstitial lung disease (4.4%). Among the patients, ten (1.3%) were diagnosed with ANCA-associated vasculitis (AAV), of whom nine had renal-limited vasculitis. Twenty-six patients tested positive for ANCA without any evidence of AAV. Of these false positives, 10 (38.4%) were human immunodeficiency virus (HIV) positive, 3 (11.5%) had tuberculosis (TB), and 3 (11.5%) had other autoimmune diseases. The annual cost of ANCA tests amounted to ZAR274,046, with ZAR17,490 spent on duplicate testing and ZAR208,275 on non-indicated clinical conditions. The study revealed that ANCA testing was performed outside standard guidelines in three-quarters of requests, and duplicate testing was common, resulting in large cost implications. Chronic infections, such as HIV and TB, and autoimmune conditions accounted for half of the false-positive tests. The findings suggest that training of clinicians is likely to reduce unnecessary tests.

Keywords: Anti-neutrophil cytoplasmic antibody, ANCA-associated vasculitis, Gated testing

1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCAs) are important diagnostic tools for ANCA-associated vasculitis (AAV), a group of necrotizing small vessel vasculitis characterized by few or no immune deposits. Due to the high false-positive rate for indiscriminate ANCA testing, the International Consensus Statements of 1999 and 2017 provided clinical guidelines of indications for ANCA testing (**Table 1**) [1,2]. The aim of these guidelines is to increase the positive predictive value (PPV) of ANCA testing by limiting the test to patients with clinical features suggestive of AAV. It has been shown that ANCA tests have a PPV of 54% and a negative predictive value (NPV) of 99% in conventional clinical settings, but with the application of guidelines, PPV is increased to

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Table 1. 1999 international consensus statement guidelines of indications for ANCA testing* [1]

i.	Glomerulonephritis, especially rapidly progressive GN
ii.	Pulmonary hemorrhage, especially pulmonary renal syndrome
iii.	Cutaneous vasculitis with systemic features
iv.	Multiple lung nodules
v.	Chronic destructive disease of the upper airways
vi.	Long-standing sinusitis or otitis
vii.	Subglottic tracheal stenosis
viii.	Mononeuritis multiplex or other peripheral neuropathies
ix.	Retro-orbital mass
x.	Scleritis

Note: *when there is no other obvious cause.

62% [3]. Encouragingly, studies show that AAV is seldom missed when testing is restricted to indications listed in the 1999 clinical guidelines [3].

AAV seems to be rare in African populations. Only a limited number of studies on ANCA antibodies or AAV in Africa have been reported, most likely due to a combination of a low index of suspicion of AAV and a lack of appropriate laboratory facilities [4]. Among a group of 60 West Africans, 6.7% of patients with chronic infections (tuberculosis [TB] and malaria) tested positive for anti-myeloperoxidase (MPO). In contrast, no ANCA antibodies were detected among healthy Africans [5].

The rising cost of laboratory investigations and equitable distribution of healthcare resources has become important issues worldwide, with both social and political implications. In South Africa, cost-effectiveness is a major criterion in developing clinical policies. We audited all ANCA tests ordered in a tertiary academic hospital to assess adherence to indications for testing, evaluate the diagnostic accuracy of the test, and review the positive ANCA test results, aiming to decrease hospital costs and avoid inappropriate specialist referrals. The Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, approved the study (HREC reference number 443/2018).

2. Methods

A retrospective record review was performed on all ANCA tests ordered through the National Health Laboratory Services (NHLS) at a state-sector tertiary hospital over 12 months. Case records were reviewed, and clinical and demographic features (including self-reported ethnic group), the department requesting the test, and comorbidities were collated. The indication for each ANCA test was assessed against the International Consensus Statement of 1999.

The revised 2017 international consensus on ANCA testing recommends the use of high-quality immunoassays as the preferred first screening method for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis [2], which remains unchanged in the 2020 consensus statement [6]. The recommendations were based on a multi-center European Vasculitis Study Group evaluation which demonstrated that these assays had a higher diagnostic performance in comparison to manual and automated indirect immunofluorescence [7].

While the consensus statement does not specify a particular type of immunoassay to be used, a recent review from the Netherlands has indicated that, for routine screening, diagnosis, and follow-up, quantitative assays measuring ANCA levels are associated with higher likelihood ratios and a more definitive diagnosis [8]. On the other hand, qualitative immunoassays can be used for confirmation and rapid testing [8], generally interpreted using a single cut-off value.

The NHLS utilized a fluorescence enzyme-linked immunosorbent assay sandwich immunoassay for ANCA testing. The specific method employed was the EliA IgG assay, performed on the Phadia 250 (Thermofisher). This *in vitro* qualitative measurement detects IgG antibodies directed against proteinase 3 (PR3) and MPO in human sera. Before analysis, the sample preparation includes allowing the serum to clot at room temperature, followed by centrifugation at 2200× g for 15 min. The serum is then drawn off, and aliquots are transferred into appropriately labeled tubes. The aliquot samples are immediately analyzed. The cutoff values (as per kit manufacturer) for anti-PR3 and anti-MPO are 1.9 U/ml and 3.4 U/ml, respectively.

Descriptive statistics and normally distributed variables are presented as means with standard deviations, and sensitivity, specificity, PPV, and NPV were calculated. Analysis was conducted using IBM SPSS Statistics V26.

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3. Results

Of 945 ANCA tests performed, 790 clinical records were identified and reviewed, while 155 patient records were missing (**Figure 1**). Among the patients, 62 had undergone multiple tests, resulting in a total of 133 duplicate tests. Most tests were ordered for inpatients (63.0%). Overall, only 193 patients (24.4%) had indications that met the 1999 guidelines for ANCA testing. The remaining 597 (75.6%) did not meet the guidelines criteria.

The departments that requested the most ANCA tests were Medicine, Ophthalmology, Neurology, and Surgery. Notably, surgery had 98.9% of its tests ordered for non-guideline indications (**Table 2**). The most common clinical problems for which ANCA tests were ordered outside of guideline indications included critical limb ischemia (9.6%), stroke (7.3%), uveitis (5.7%), acute kidney injury (4.9%), and interstitial lung disease (4.4%). On the other hand, the most common guideline indications were glomerulonephritis (GN) (52.1%), peripheral neuropathy (19.0%), scleritis (10.5%), and cutaneous vasculitis (9.0%).

Ten patients (1.3%) were diagnosed with AAV over the 12 months, and these patients were predominantly female, of mixed racial ancestry, with a mean (SD) age of 54.5 (16.4) years (**Table 3**). One patient was diagnosed with ANCA-negative granulomatosis with GPA, and nine had renal-limited vasculitis (RLV) with pauci-immune necrotizing GN on renal biopsy and no extra-renal manifestations. Only five of the RLV patients were ANCA-positive (mostly MPO-positive).

Of all ANCA tests performed, 31 patients (3.9%) had tested positive for ANCA, of which 5 were true positives and 26 were false positives showing no evidence of AAV. Of these false positives, 11 (42.3%) were associated with chronic infections, such as human immunodeficiency virus (HIV), TB, and syphilis, while three (11.5%) had autoimmune diseases (**Table 4**). There was no explanation for the positive results in 13 patients (50%). In terms of drug-induced ANCA positivity, no commonly associated drugs, including anti-thyroid drugs, D penicillamine, sulfasalazine, allopurinol, cocaine, or TNF inhibitors, were implicated in the false-positive ANCA group. The sensitivity, specificity, PPV, and NPV for the total cohort were 50.0%, 96.7%, 16.1%, and 99.3%, respectively.

Of the 193 ANCA tests which met guideline indications for testing, 14 patients tested positive for ANCA, of which five were true positive, while the remaining nine were false positives, showing no evidence of AAV. When focusing only on patients who met the guideline indications for testing, the PPV improved, although it remained

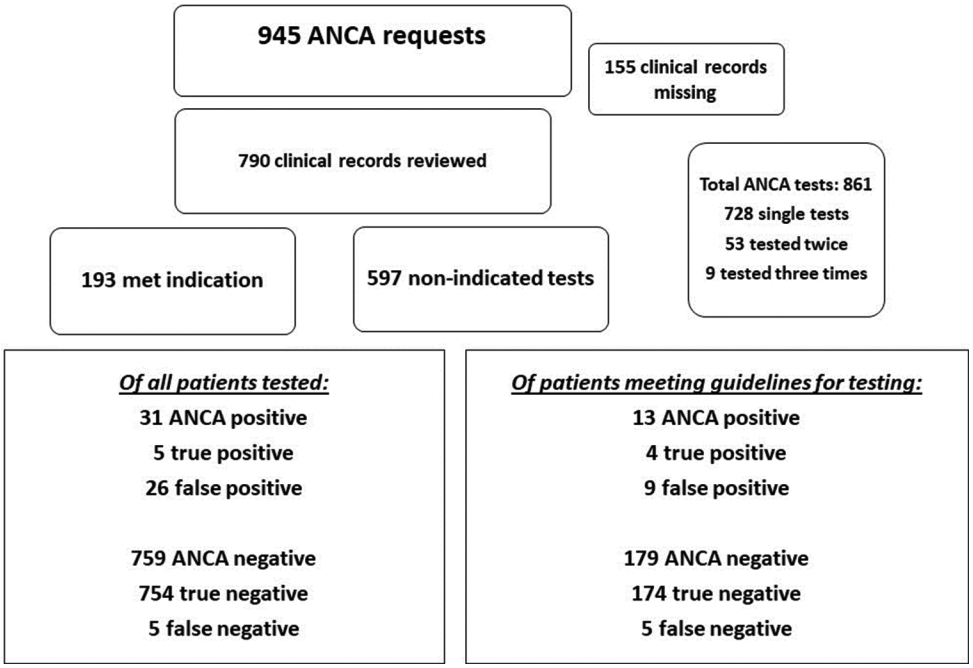


Figure 1. Flow diagram of anti-neutrophil cytoplasmic antibody tests performed over 12 months at a tertiary hospital in South Africa.

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Table 2. ANCA testing according to indication guidelines per department

Department	Total requests *n*=790	1999 Guideline indication		Common non-guideline indications
		No *n*=598 *n* (%)	Yes *n*=192 *n* (%)	
Cardiology	4	4 (100)	0 (0)	Valvular heart disease
Critical care	22	15 (68.2)	7 (31.8)	AKI, seizures, encephalopathy
Dermatology	10	6 (60.0)	4 (40.0)	Non-specific rash
Otolaryngology	31	27 (87.1)	4 (12.9)	Sensory-neural hearing loss, vocal cord paralysis
Gastroenterology	3	3 (100)	0 (0)	IBD
General Medicine	272	173 (63.6)	99 (36.4)	AKI, stroke
Nephrology	30	15 (50.0)	15 (50.0)	AKI
Neurology	100	70 (70.0)	30 (30.0)	Stroke, encephalopathy
Obgyn	25	20 (80.0)	5 (20.0)	Recurrent pregnancy losses, POF
Ophthalmology	105	83 (79.1)	22 (20.9)	Uveitis, optic neuritis
Orthopedics	28	28 (100)	0 (0)	Trigger finger, CTS, arthritis
Psychiatry	2	2 (100)	0 (0)	Encephalopathy, psychosis
Pulmonology	35	32 (91.4)	3 (8.6)	ILD, poorly controlled asthma, PHT
Rheumatology	25	23 (92.0)	2 (8.0)	Raynaud's phenomenon, arthritis
Surgery	95	94 (98.9)	1 (1.1)	CLI, vascular aneurysms
Trauma	3	3 (100)	0 (0)	ICA dissection, TBI

Abbreviations: AKI: Acute kidney injury, CLI: Critical limb ischemia, CTS: Carpal tunnel syndrome, IBD: Inflammatory bowel disease, ICA: Internal carotid artery, ILD: Interstitial lung disease, Obgyn: Obstetrics and gynecology, PHT: Pulmonary hypertension, POF: Premature ovarian failure, TBI: Traumatic brain injury.

Table 3. Details of ten patients with anti-neutrophil cytoplasmic antibody-associated vasculitis

Gender	Age	Ethnicity	Department	AAV type	MPO	PR3	Guideline indication
M	55	Mixed	Medicine	GPA	Neg	Neg	Yes
F	49	Mixed	Medicine	RLV	Pos	Neg	Yes
F	37	Mixed	Medicine	RLV	Pos	Neg	Yes
M	81	Caucasian	Medicine	RLV	Pos	Neg	Yes
F	71	Mixed	Medicine	RLV	Pos	Neg	Yes
M	39	Mixed	Medicine, Nephrology	RLV	Neg	Pos	Yes
F	58	African	Medicine, Nephrology	RLV	Neg	Neg	Yes
F	58	Mixed	Nephrology	RLV	Neg	Neg	Yes
F	29	Mixed	Nephrology	RLV	Neg	Neg	Yes
F	68	Mixed	Medicine	RLV	Neg	Neg	Yes

Abbreviations: AAV: Anti-neutrophil cytoplasmic antibody-associated vasculitis, F: Female, GPA: Polyangiitis, M: Male, MPO: Anti-myeloperoxidase antibody, Neg: Negative, Pos: Positive, PR3: Anti-proteinase 3 antibody, RLV: Renal limited vasculitis.

lower than what has been described elsewhere due to the high number of false positive tests observed in our setting. The sensitivity, specificity, PPV, and NPV were 50.0%, 95.1%, 35.7%, and 97.2%, respectively. The total estimated cost of ANCA tests throughout the year amounted to ZAR274,046, with ZAR17,490 spent on duplicate testing and ZAR208,275 on tests for non-indicated clinical conditions**.**

4. Discussion

Due to its multi-system heterogeneous presentation, insidious onset, and rarity, small vessel vasculitis poses a diagnostic challenge. As a result, the ANCA

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Table 4. Positive anti-neutrophil cytoplasmic antibody results in patients with no evidence of anti-neutrophil cytoplasmic antibody-associated vasculitis

Gender	Age	Ethnicity	MPO	PR3	Guideline indication	Indication description	Clinical information
M	47	African	Pos	Neg	Yes	GN	HIV, AKI due to hypertension nephrosclerosis
F	48	African	Pos	Neg	Yes	GN	HIV, HIVAN
F	43	African	Pos	Neg	No	Hepatitis	HIV, confirmed DILI
F	33	Mixed	Neg	Pos	No	Hepatomegaly and lymphadenopathy	HIV, HIV seroconversion
M	47	Mixed	Neg	Pos	No	Cholangitis	HIV, syphilis, confirmed liver abscesses
F	44	African	Pos	Pos	Yes	Palpable purpura	HIV, biopsy- cutaneous lupus
M	35	African	Neg	Pos	Yes	GN	TB, AKI, and macroscopic haematuria
F	38	African	Pos	neg	No	AKI	HIV, disseminated TB
F	30	African	Pos	Neg	Yes	PN	HIV, TB
M	39	African	Pos	Neg	No	Valve heart disease	HIV, TB, epilepsy
F	57	Mixed	Neg	Pos	No	Seizures	HPT, syphilis
F	80	Mixed	Pos	Neg	No	ILD	RA, HPT, hyperthyroidism
M	38	Caucasian	Pos	Neg	No	Hepatitis	AIH
F	55	African	Pos	Neg	No	Unclear	SLE
M	67	Mixed	Pos	Neg	Yes	GN	HPT, biopsy- diffuse glomerulosclerosis
F	69	Mixed	Pos	Neg	Yes	GN	HPT, DM, asthma, biopsy-MCGN, and ATN
M	47	African	Pos	Neg	No	AKI	-
F	62	Mixed	Pos	Neg	Yes	PN	HPT, ILD
F	68	Mixed	Pos	Neg	No	Myelopathy	HPT
F	73	Mixed	Pos	Neg	No	ILD	HPT, DM
F	54	Mixed	Pos	Neg	No	Poorly controlled asthma	HPT, asthma
M	29	African	Pos	Pos	No	Uveitis	-
M	66	Mixed	Neg	Pos	Yes	Scleritis	HPT
M	41	Asian	Neg	Pos	No	Amblyopia	-
F	48	Mixed	Neg	Pos	No	Raynaud's phenomenon	Breast cancer in remission
F	38	African	Pos	Neg	No	POF	-

Abbreviations; AIH: Autoimmune hepatitis. AKI: Acute kidney injury, ATN: Acute tubular necrosis, DILI: Drug-induced liver injury, DM: Diabetes mellitus, F: Female, GN: Glomerulonephritis, HIV: Human immunodeficiency virus, HIVAN: HIV associated nephropathy, HPT: Hypertension, ILD: Interstitial lung disease, LN: Lupus nephritis, M: Male, MCGN: Mesangiocapillary glomerulonephritis, MPO: Anti-myeloperoxidase antibodies, Neg: Negative, PN: Peripheral neuropathy, POF: Premature ovarian failure, Pos: Positive, PR3: Anti-proteinase 3 antibodies, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, TB: Tuberculosis.

test plays an important role as a screening tool. However, our study revealed that only a quarter of ANCA tests conducted had indications that met the 1999 international consensus statement guidelines. This indiscriminate use of ANCA testing is costly and lowers the test sensitivity and PPV. Similar studies conducted elsewhere reported that 33.4% and 50.0% of ANCA tests were performed within guideline indications [9,10]. Implementing gating policies to restrict ANCA testing has proven

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beneficial, reducing false-positive rates by up to 27.0% and increasing ANCA positivity by 11.8% without missing AAV cases [3,11].

False-positive ANCA tests have been well-described, and in the present study, they resulted in a lower PPV than what has been described elsewhere [10,12-14]. In our study, among the 26 patients who tested positive for ANCA but showed no evidence of AAV, chronic infection was noted in 42.3% of the cases. Elsewhere, chronic infections, including TB, malaria, leprosy, suppurative lung disease, infective endocarditis, hepatitis B and C, and HIV, have been noted to cause positive ANCA results [5,15]. In the pre-highly active antiretroviral therapy (HAART) era, Koderisch *et al*. described c-ANCA positivity in 24 out of 29 HIV-infected patients (83.0%) [16]. More recently, among HIV patients with a well-controlled viral load on HAART, 45.0% had at least one autoantibody present, especially ANA (33.0%) and ANCA (13.0%), without clinically relevant disease [17].

In the present study, 11.5% of false positive ANCA tests were observed in patients with autoimmune diseases, which are consistent with findings reported elsewhere, particularly among patients with chronic autoimmune hepatitis (70.0%), rheumatoid arthritis, and systemic lupus erythematosus (20.0%) [18]. Other causes of positive ANCA results, including certain medications (anti-thyroid drugs, propylthiouracil, levamisole-adulterated cocaine, minocycline and hydralazine), and inflammatory bowel disease, have been described but were not encountered in our study. The high rate of false positive results underscores the need to increase the pre-test probability by limiting ANCA testing to the 1999 international consensus statement guidelines.

Our study shows a very low rate of PR3 positivity: only nine patients in the false-positive group and one in the confirmed AAV group tested positive for PR3. We believe that this finding reflects the low rate of positive tests in African populations. Therefore, we plan to conduct more prospective studies to further investigate this phenomenon.

The AAV group was predominantly RLV, with half of these patients showing positive ANCA serology. Elsewhere, ANCA-negative RLV has been well-documented, highlighting the importance of tissue diagnosis as the gold standard when small vessel vasculitis is highly suspected [19]. The ANCA-negative group exhibits poorer renal outcomes and less extrarenal involvement.

Limitations of this study include the imprecision of retrospective record review where clinician notes may have inadequately documented the test indication, together with a large number of missing records. In addition, this audit was conducted in a tertiary hospital, and the results are not generalizable to other health-care platforms.

5. Conclusions

Our study shows indiscriminate ANCA testing, with 75.6% of tests done outside of guideline indications, and duplicate testing, with large cost implications. We also demonstrated false positive tests resulting in a lower PPV than described elsewhere. Implementing restrictive protocols for ANCA testing according to the 1999 testing guidelines, together with the training of clinicians, is likely to reduce unnecessary tests, resulting in significant cost savings and a reduction in inappropriate referrals to sub-specialists.

Acknowledgments

The authors thank Dr. Nasreen Akoo and Dr. Leandi Steynfaardt for assistance with data collection and Dr. Misha Jivan for statistical analysis.

Funding

None.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contributions

Conceptualization: All authors
Investigation: All authors
Writing-original draft: All authors
Writing-review and editing: All authors

Ethics Approval and Consent to Participate

Ethics approval was obtained for this study from The Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape

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Town, approved the study (HREC reference number 443/2018).

Consent for Publication

Not applicable.

Availability of data

Data can be obtained from the corresponding author following formal request.

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