WHEN TO CHECK ANTI-NUCLEAR ANTIBODY (ANA)

TARGET AUDIENCE	Primary and secondary care
PATIENT GROUP	Adult patients

Clinical Guidelines Summary

- Connective tissue diseases (CTD) cover a wide range of autoimmune diseases. They are often associated with particular autoantibodies.
- The 'classic' CTDs include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (or scleroderma), polymyositis and dermatomyositis.
- Patients may present with a variety of symptoms and these can vary greatly between individuals.
- In those who have a suspected connective tissue disease ANA should be checked
- This guideline outlines
    - the clinical features associated with connective tissue diseases where ANA should be checked
    - further guidance regarding how to interpret ANA results
    - when to refer patients to rheumatology for further advice.

Guideline Body

Clinical Features Associated with Connective Tissue Diseases

History

- Photosensitive skin rash
- Poly arthralgia or polyarthritis
- Muscle pain and weakness
- Mouth ulcers
- Dry eyes and/or dry mouth
- Raynaud's phenomenon
- Hair loss
- Pleurisy
- Dyspnoea
- Recurrent miscarriages

Examination

- Skin rash
- Synovitis
- Mouth ulcers
- Sclerodactyly / scleroderma
- Scarring alopecia
- Raynaud's phenomenon
- Digital ulceration
- Telangiectasia
- Pleural or pericardial effusion

Helpful investigations

- FBC with anaemia, leucopaenia or thrombocytopaenia
- Raised ESR
- Strongly positive ANA and positive anti-dsDNA

Interpretation of ANA test results

- ANA testing has a high degree of sensitivity (>95%) for SLE and other connective tissue diseases; however, the utility of the test is limited by very low specificity (<60%) which severely limits its value in the investigation of patients who have only non-specific symptoms. Consequently, the ANA test is not a good screening test for SLE or other autoimmune diseases.
- The clinical value of an ANA test is tremendously enhanced by testing when there is a reasonable pre-test probability (i.e. clinical suspicion) of a connective tissue disease.

When to check Anti-Nuclear Antibody

- One reason that the specificity of the ANA test is low is that ANA can also be found in non-rheumatic inflammatory diseases such as autoimmune hepatitis, primary biliary cirrhosis, Crohn's disease, chronic infectious diseases (TB, SBE, infectious mononucleosis) and lymphoproliferative disorders. ANA can also be induced by many drugs.
- **Drugs associated with ANA production and lupus-like disease**

Procainamide	D-penicillamine	Terbinafine	Hydralazine
Isoniazid	Minocycline	Quinidine	Methyldopa
Phenytoin	Chlorpromazine	Anti-TNF agents	

Clinical significance

- **ANA Titres**
  - Clinically significant titres of ANA are usually >1:160
    - ANA 1:40 occur in 20 – 30% of normal healthy individuals
    - ANA 1:80 occur in 10 – 15% of normal healthy individuals
    - ANA 1:160 occur in 5% of normal healthy individuals
    - ANA 1:320 occur in 3% of normal healthy individuals
  - In the elderly, over 70 years, up to 70% have a positive ANA of 1:40
  - 'False positive' ANA results up to 1:80/1:160 (and sometimes beyond) are relatively non-specific and, in themselves, not highly indicative of a connective tissue disorder.
- **Anti-dsDNA antibody**
  - Anti-dsDNA antibody testing is performed as a reflex by the laboratory where the ANA screening test is found to be significantly positive. Anti-dsDNA antibodies are principally associated with lupus.
  - Anti-dsDNA levels up to 75 IU/ml are considered as negative and not suggestive of lupus, particularly where relevant clinical indicators are absent.
  - A second test (crithidia), which also detects dsDNA autoantibodies, is routinely undertaken as a safety net by the laboratory on samples where the quantitative anti-dsDNA result is >30 IU/ml to identify borderline positive samples.

Primary care management

- Manage symptoms pending clinic review

Who to refer

- Patients with several CTD symptoms or signs (typically 4 or more) who test ANA positive
- **AND** anti-dsDNA positive

Who not to refer

- Patients with arthralgia who have a positive ANA and negative anti-dsDNA, with no other symptoms and signs.

When to check Anti-Nuclear Antibody

- Patients with Raynaud's who have a positive ANA and negative anti-dsDNA, with no other symptoms or signs.
- Patients with generalized pain who have a positive ANA and negative anti-dsDNA, with no other symptoms or signs.

References/Evidence

Any content in your guideline that is either quoted, paraphrased and/or borrowed from an external source must be attributed to the original.
For published papers, Harvard referencing style is preferable

Zanussi, J.T., Zhao, J., Wei, W.-Q., Karakoc, G., Chung, C.P., Feng, Q., Olsen, N.J., Stein, C.M. and Kawai, V.K. (2023). Clinical diagnoses associated with a positive antinuclear antibody test in patients with and without autoimmune disease. BMC Rheumatology, [online] 7, p.24. doi:https://doi.org/10.1186/s41927-023-00349-4.

Abeles, A.M. and Abeles, M. (2013). The Clinical Utility of a Positive Antinuclear Antibody Test Result. The American Journal of Medicine, 126(4), pp.342–348. doi:https://doi.org/10.1016/j.amjmed.2012.09.014.

Appendices

1. Governance information for Guidance document

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Endorsing Body:	Rheumatology Consultants
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CHANGE RECORD

Date	Lead Author	Change	Version No.
30/5/24	Dr Saira Batool	*e.g. Review, revise and update of policy in line with contemporary professional structures and practice*	1
			2
			3
		.	4
			5

2.You can include additional appendices with complimentary information that doesn't fit into the main text of your guideline, but is crucial and supports its understanding.

When to check Anti-Nuclear Antibody

e.g. supporting documents for implementation of guideline, patient information, specific monitoring requirements for secondary and primary care clinicians, dosing regimen/considerations according to weight and/or creatinine clearance