

Evidence-Based Guidelines for the Use of Immunologic Tests: Antinuclear Antibody Testing

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Introduction

This article is part of a series on immunologic testing guidelines. The series introduction, published in this issue, outlines the full methodology for obtaining data, grading the literature, combining the information from multiple sources, and developing recommendations. Briefly, MEDLINE and Healthstar were searched using a variety of search terms, and all relevant available literature was reviewed. All articles were critically reviewed using published standards for studies of diagnostic tests. Test use was categorized as primarily diagnostic or prognostic (which also included monitoring). Information was extracted from each article to allow for calculation of a weighted average for sensitivity and specificity; likelihood ratios (LRs) were then derived from these values (positive LR = sensitivity / [1-specificity]; negative LR = [1-sensitivity] / specificity). Recommendations for use of tests were based on the LRs, where a test was considered to be “very useful” for a given disease if the weighted average positive LR was > 5 or negative LR was < 0.2 . A test was considered “useful” if the weighted average positive LR was > 2 and ≤ 5 or negative LR was > 0.2 and ≤ 0.5 . A test

was considered “not useful” if the positive LR was ≤ 2 or the negative LR was > 0.5 .

Definition

Antinuclear antibodies (ANA) directed against a variety of nuclear antigens have been detected in the serum of patients with many rheumatic and nonrheumatic diseases, as well as in patients with no definable clinical syndrome. These antibodies can be detected using a variety of substrates and staining techniques as described below and are directed against many different nuclear antigens.

Background

Hargraves described the lupus erythematosus (LE) cell in the blood of patients with systemic lupus erythematosus (SLE) in 1948 (1). Although the LE cell preparation was the first test that facilitated the laboratory diagnosis of SLE, it soon became evident that some patients with clinical SLE had negative LE cell tests and some people had positive LE cell tests but did not have SLE. In an attempt to improve the sensitivity and specificity of tests for the diagnosis of SLE, techniques were developed to characterize the LE cell factor(s), which were soon recognized to be a family of antibodies to nuclear constituents. A number of immunochemical techniques were utilized to detect and characterize these antinuclear antibodies (ANA). These methods include immunofluorescence microscopy (i.e., ANA/ANF tests that use rodent liver or kidney, human cell lines, and other substrates), immunodiffusion (i.e., Ouchterlony and counterimmunoelectrophoresis), hemagglutination, complement fixation, solid-phase immunoassays (i.e., enzyme-linked immunosorbent [ELISA] or immunoblotting), and radioimmunoassays. Tests have used whole cells (i.e., ANA), partially purified nuclear antigens (i.e., immunodiffusion), or highly purified or recombinant nuclear antigens (i.e., ELISA assays).

Methods. ANA results vary widely depending on the substrate and immunohistochemical methods used for detection. The technique most widely described in the current literature is immunofluorescent microscopy performed on rodent kidney or liver cells, or human epithelial-2 (HEp-2) cells. The HEp-2 cell line is derived

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Submitted for publication September 6, 2001; accepted in revised form March 10, 2002.

from a human epithelial cell tumor. Because the cells are identical, they provide a standardized substrate for detecting ANA. ANAs performed on HEp-2 cells are more frequently abnormal in patients with any ANA-associated disease (i.e., improved sensitivity), but more patients without any ANA-associated disease will have abnormal results (i.e., lower specificity). Variability in ANA test results may be introduced through any of the following: potency of the fluorescein tagged anti-gamma globulin; specificity of the anti-gamma globulin (e.g., anti-IgG, IgA, IgM); and strength of the UV bulb in the fluorescent microscope. Another variable that effects the reliability of ANA testing is the recent introduction of ELISA technology. Currently, there is not much published data on the performance of ANA tests performed using an ELISA, however the few published reports suggest that the ELISA has a high incidence of false positive results (2,3). Before clinicians depend on the results of ANA testing performed with ELISA technology, more widespread testing should be performed.

A practice that has been advocated for sera found to be positive on ANA testing is for the automatic subsequent testing of panels of other autoantibodies. This "reflex testing" or "cascade testing" has been suggested to speed diagnosis and enhance diagnostic accuracy. Very few studies have addressed the utility of such a practice. Although patterns of results to multiple autoantibody testing might be associated with different diseases, the utility depends to a large extent on the populations assessed (4,5). In addition, it remains to be proven that cascade testing offers advantages over focused testing of specific autoantibodies based on clinical suspicion. Therefore, until this approach has been proven in rigorous studies, it cannot be recommended.

Testing in healthy controls and relatives. Of the 17 articles found that specifically examined ANA results in healthy controls, 3 were grade "A" and are included in this review (6–8). Data from these articles suggest that healthy controls will have positive ANA tests at lower titers, such that 25–30% of healthy controls were reported to have an ANA titer of 1:40, 10–15% at 1:80, and 5% at 1:160 or greater. With increasing age, particularly in women, this frequency increases (9).

We identified 9 articles that examined the rate of positive ANA tests in relatives of persons with known connective tissue disease. Six were grade "A" or grade "B" and are included in the review (10–15). Relatives had ANA titers \geq 1:40 in 25–30% of cases. If one looks further, these positive ANA titers are often explained by antibodies to a number of other nuclear antigens, such as double-stranded DNA (dsDNA), Sm, Ro, La, Scl-70, and RNP. (Antibody tests for these antigens will be discussed in other articles in this series.)

Summary recommendations. ANA results should not be reported as "positive" or "negative," but must include a description of the highest titer for which immunofluorescence is detected. Additionally, laboratory reports should include a description of the percentage of patients without any ANA-associated disease (controls) who have similar titers. Because of the many potential technical problems in

the ANA tests that can affect sensitivity and specificity, negative and positive controls should be used each time the test is performed. ANA tests should no longer be performed on substrates other than HEp-2 or rodent, except in experimental situations.

Indications for the clinical use of the ANA test

After surveying the articles found in an extensive literature search, we determined which diseases would be included in this guideline. There were data available to determine the ANA testing characteristics for all common systemic rheumatic diseases. Also, there was adequate information regarding the use of ANA testing in autoimmune hepatitis, multiple sclerosis, idiopathic thrombocytopenic purpura, autoimmune thyroid disease, and fibromyalgia.

Systemic lupus erythematosus. Diagnosis. The literature search identified 65 articles that dealt with ANA testing for the diagnosis of SLE; 27 (42%) were excluded for a variety of reasons. Exclusion criteria included: nonrandom or nonconsecutive patient selection ($n = 18$), no clear reference standard ($n = 8$), and ANA not tested in serum ($n = 1$). Of the 38 remaining studies 21 were grade "A," 4 were grade "B," and the remaining 14 "C" or "D." Fourteen of the grade "A" studies used rodent substrate (mouse or rat) and the remaining 6 used HEp-2; these grade "A" studies were included in the analyses (Table 1) (16–36).

The control populations used in the included studies varied from healthy blood donors to patients with other connective tissue diseases. Because the specificity of a test is based on the rate of positive results in the control population, selection of a relevant control group is critical. Rates of negative ANA testing for controls (specificity) was 49% in patients with other connective tissue diseases, 75% in patients with nonconnective tissue rheumatic disease, and 78% in other controls (Table 2). After combining all non-SLE patients, the average sensitivity of the ANA was 93% and the specificity was 57%. The positive likelihood ratio was 2.2 and the negative likelihood ratio was 0.1 for diagnosing SLE.

Because of the high sensitivity of the ANA for SLE, almost all patients with SLE will have a positive ANA test. However due to the low prevalence of SLE in the general population (40–50 cases per 100,000 persons), most people with positive ANAs do not have SLE (positive predictive value of 11%). A negative ANA helps to rule out SLE because it is a very sensitive test. In most patients suspected of having SLE, the ANA is the best initial laboratory test. Positive ANAs must be interpreted in the clinical context. In order to appropriately estimate the posttest probability of SLE, a clinician must accurately gauge the pretest disease probability (37). Patients with few signs or symptoms of SLE have a low pretest probability. Positive tests in such patients are often of unclear clinical significance.

Summary recommendations: When there is a strong clinical suspicion that a patient has SLE, the ANA is the best diagnostic laboratory test to obtain. Because the ANA is present in many healthy persons and patients with a

Table 1. Grade "A" Studies of the ANA for diagnosis of systemic lupus erythematosus*

Author, year (ref.)	Study population	Diagnoses	No.	No. pos ANA	No. neg ANA
Weitzman, 1977 (16)	Selected SLE with dsDNA	SLE	48	46	2
Sulcebe, 1992 (17)	Unselected inpatients and ambulatory patients	SLE	102	96	6
		RA	595	125	470
		SSc	59	31	28
		Raynaud's	38	12	26
		PM-DM	29	8	21
		Overlap	61	29	32
		Sjögren's	10	6	4
		Cutaneous vasculitis	34	8	26
		Arthralgias	93	3	90
		OA	85	5	80
		Nonrheumatic	283	42	241
Davis, 1989 (18)	Selected patients from rheumatology clinic	SLE	37	17	20
		RA	67	18	49
		SSc	4	1	3
		PM-DM	9	4	5
Subcommittee for scleroderma Criteria, 1980 (19)	Population used for scleroderma criteria development	SLE	158	150	8
		SSc	384	215	169
		PM-DM	112	35	77
		Raynaud's	113	35	78
Chudwin, 1983 (20)	All patients seen in pediatric rheumatology clinic with a positive ANA	SLE		37	
		Discoid LE		2	
		JRA		33	
		Sjögren's		9	
		MCTD		7	
		DM		3	
		Nonrheumatic		47	
Calvo-Alen, 1996 (21)	Undifferentiated CTD via Cooperative Clinics	SLE	18	12	6
		Other CTD	125	66	59
Ginsburg, 1983 (22)	Patients evaluated in rheumatology clinic	SLE	130	130	0
		Overlap	117	95	22
Rothfield, 1968 (23)	Unclear which SLE patients	SLE	47	47	0
		SSc	47	28	19
Arroyave, 1988 (24)	Pediatric population with controls chosen from surgery clinic	Controls	241	4	237
Jonsson, 1988 (25)	All patients with SLE in a Swedish health district	SLE	80	79	1
Hochberg, 1985 (26)	SLE patients followed at Johns Hopkins	SLE	150	141	9
Arnett, 1990 (27)	Selected cases of CTD and community controls	SLE	30	26	4
		SSc	15	11	4
		PM	3	1	2
		UCTD	9	8	1
		Relatives	69	23	46
		Controls	53	19	34
Schur, 1974 (28)	Patients with suspected rheumatic disease	SLE	228	228	0
		RA	448	314	134
		JRA	162	78	84
		SSc	28	23	5
		Sjögren's	42	27	15
Koh, 1994 (29)	Selected patients in a rheumatology division	SLE	147	139	8
Nisengard, 1975 (30)	Selected patients from rheumatology division and blood donors	SLE	24	21	3
		RA	20	7	13
		SSc	15	15	0
		MCTD	4	4	0
		Controls	134	18	116
Mulli, 1977 (31)	Hospitalized rheumatology patients and hospitalized controls	SLE	64	64	0
		SSc	30	27	3
		Sjögren's	31	13	18
		Other CTD	10	2	8
		Controls	53	0	53
		Blood donors	90	88	2

(continued)

Table 1. Grade "A" Studies of the ANA for diagnosis of systemic lupus erythematosus* (Continued)

Author, year (ref.)	Study population	Diagnoses	No.	No. pos	No. neg
				ANA	ANA
Speransky, 1987 (32)	Selected patients from rheumatology division	SLE	76	56	20
		SCLE	31	17	14
		Sicca	20	5	15
Chellingworth, 1984 (33)	Selected patients from rheumatology division	SLE	49	43	6
		RA	297	146	151
		SSc	11	8	3
		Other CTD	189	57	132
		OA	34	8	26
		Primary Raynaud's	36	17	19
Rooij, 1985 (34)	Selected patients from rheumatology division	SLE	37	35	2
		SSc	31	25	6
		Sjögren's	8	7	1
		RA	16	14	2
		PM-DM	5	4	1
Kallenberg, 1980 (35)	Patients referred for Raynaud's phenomenon	Secondary Raynaud's	8	8	0
		Primary Raynaud's	83	48	35
		SLE	55	52	3
Clegg, 1991 (36)	Cooperative Clinics study patients	RA	55	20	35
		SSc	43	42	1
		PM-DM	37	20	17

* ANA = antinuclear antibody; SLE = systemic lupus erythematosus; dsDNA = double-stranded DNA; RA = rheumatoid arthritis; SSc = systemic sclerosis; PM-DM = polymyositis-dermatomyositis; Overlap = overlap syndrome; OA = osteoarthritis; nonrheumatic = controls without rheumatic disease; JRA = juvenile RA; MCTD = mixed connective tissue disease; CTD = connective tissue disease; UCTD = undifferentiated connective tissue disease; JCA = juvenile chronic arthritis.

multitude of other diseases, it should not be used as a test to rule out rheumatic disease. If the ANA is positive, antibody tests to other specific antigens might be considered depending on the clinical setting. Tests for antibodies to dsDNA or extractable nuclear antigens should not be requested before a positive result on the ANA is obtained. Data pertaining to extractable nuclear antigens will be presented in future articles in this series.

Monitoring/prognosis. There are few data suggesting a correlation between ANA titer and disease activity for patients with SLE. Thus, serial ANA testing is of unknown value in patients with a known positive ANA. Serial testing for specific antibodies, such as anti-dsDNA, may have

clinical utility. This will be discussed further in future articles in this series.

Systemic sclerosis. Diagnosis. Patients with systemic sclerosis usually present with a distinct set of clinical signs and symptoms, and a positive ANA is not part of the clinical criteria for this disease. Sixty-nine articles related to ANA testing for systemic sclerosis (SSc) were identified through the literature search. Nineteen were excluded because of nonrandom or nonconsecutive patient selection ($n = 3$) or no clear reference standard ($n = 16$). Of the remaining 50 studies, 30 were grade "A," 10 were grade "B," and 10 were grade "C" or "D." Eight of the grade "A"

Table 2. Diagnostic test accuracy of the antinuclear antibody for major rheumatic diseases*

Disease	No. studies considered	Sensitivity overall (%)	Specificity			Overall (%)	Likelihood ratio	
			Other CTD (%)	Non-CTD rheumatic (%)	Healthy (%)		Pos	Neg
SLE	21	93	49	75	78	57	2.2	0.11
SSc	30	85	44	75	71	54	1.86	0.27
PM-DM	14	61	52	91	82	63	1.67	0.61
Sjögren's	16	48	44	91	71	52	0.99	1.01
Raynaud's†	12	64	48	8	15	41	1.08	0.88
JCA	21	57	na	na	na	39	0.95	1.08
JCA with uveitis	21	80	na	na	na	53	1.68	0.39
RA	14	41	38	85	82	56	0.93	1.06

* na = data not available; see table 1 for additional definitions.
† These values refer to the ability of the ANA to distinguish secondary from primary Raynaud's phenomenon.

studies used rodent substrate (mouse or rat) and the remaining 22 used HEp-2. All grade "A" studies were included in the analyses (Table 3 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (17–19, 23,24,27,28,30,31,33–36,38–54).

Similar to studies of the ANA in SLE, the control populations varied widely. Some studies had healthy blood donors as controls and other studies used patients with other connective tissue diseases. Rates of negative ANA testing in controls (specificity) was 44% in patients with other connective tissue diseases, 75% in patients with nonconnective tissue rheumatic disease, and 72% in other controls (Table 2). The sensitivity was 85% among all grade "A" articles and specificity was 54%. The positive likelihood ratio was 1.9 and the negative likelihood ratio was 0.3.

Summary recommendations: Patients suspected of having systemic sclerosis should have an ANA test performed because a negative result would prompt consideration of other fibrosing illnesses, such as eosinophilic fasciitis or linear scleroderma.

Monitoring/prognosis. There are few data suggesting a correlation between ANA titer and activity of disease in patients with SSc. Thus, serial ANA testing of patients with a known positive ANA is of unknown value. Specific autoantibodies, such as the Scl-70 and anti-centromere, may have prognostic significance. This will be discussed further in future articles in this series.

Summary recommendations: ANA testing should not be used to assess the disease activity of patients with SSc.

Idiopathic inflammatory muscle disease (polymyositis and dermatomyositis). *Diagnosis.* The ANA is not part of the diagnostic criteria for idiopathic inflammatory muscle disease, but is commonly found in association with it. Twenty-seven articles related to ANA testing for polymyositis (PM) or dermatomyositis (DM) were identified through the literature search. Three were excluded because of nonrandom or nonconsecutive patient selection and 4 due to the absence of any clear reference standard. Of the remaining 20 studies, 13 were grade "A," 3 were grade "B," and 4 were grade "C" or "D." Three of the grade "A" studies used rodent substrate (mouse or rat) and the remaining 10 used HEp-2. All of the grade "A" studies were included in the analyses (Table 4 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (17–20,27,34,36,55–60).

Similar to studies of the ANA in SLE, the control populations varied widely. Some studies had healthy blood donors as controls and other studies used patients with other connective tissue diseases. The rate of negative ANA testing in controls (specificity) was 52% in patients with other connective tissue diseases, 91% in patients with nonconnective tissue rheumatic disease, and 82% in other controls (Table 2). The sensitivity averaged across all grade "A" articles was 61% and the specificity was 63%. The positive likelihood ratio was 1.7 and the negative likelihood ratio was 0.6.

Summary recommendations: A positive ANA in patients with signs and symptoms of inflammatory muscle disease

is only weak evidence of PM or DM. Current evidence suggests that the ANA is not useful for diagnosis of PM or DM, and that other connective tissue diseases (SLE or overlap syndrome) must also be considered. A negative test should not dissuade a clinician from further workup.

Monitoring/prognosis. There are few data suggesting a correlation between ANA titer and activity of disease in patients with PM or DM. Thus, in patients with a known positive ANA, serial testing is of unknown value. Specific autoantibodies, such as the RNA synthetases may have prognostic significance.

Sjögren's syndrome. *Diagnosis.* A preliminary set of diagnostic criteria for Sjögren's syndrome consist of ocular signs and symptoms, oral signs and symptoms, salivary gland pathology, and a positive autoantibody test, including an ANA. These criteria, however, have not been validated; the conclusions from this literature review were different.

Twenty-seven articles related to ANA testing for Sjögren's syndrome were identified through the literature search. Two were excluded because of nonrandom or nonconsecutive patient selection and 4 due to the absence of any clear reference standard. Of the remaining 21 studies, 16 were grade "A," 2 were grade "B," and 3 were grade "C" or "D." Nine of the grade "A" studies used rodent substrate (mouse or rat) and the remaining 7 used HEp-2. Only the grade "A" studies were included in these analyses (Table 5 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (17,20,28,31,34,61–71).

Similar to studies of the ANA in SLE, the control populations varied widely. Some studies had healthy blood donors as controls and other studies used patients with other connective tissue diseases. Rates of negative ANA testing in controls (sensitivity) were 44% in patients with other connective tissue diseases, 91% in patients with nonconnective tissue rheumatic disease, and 71% in other controls (Table 2). The average sensitivity for the included studies was 48% and the specificity was 52%. The likelihood ratio for patients with a positive test is 0.99 and for patients with a negative test 1.01.

Summary recommendations: ANA testing is not useful for diagnosing Sjögren's syndrome. In patients with Sjögren's syndrome possibly related to SLE, an ANA can help clarify whether an underlying connective tissue disease exists.

Monitoring/prognosis. There are no data regarding the use of ANA testing to monitor the activity of Sjögren's syndrome or for determining prognosis.

Raynaud's phenomenon. *Diagnosis.* Raynaud's phenomenon is usually defined as episodic color changes of the digits, ears, or tongue in response to environmental or emotional stimuli. The color changes include pallor, cyanosis, and erythema. Because Raynaud's phenomenon is a physical examination finding, ANA testing does not help with diagnosis.

Summary recommendations: Raynaud's phenomenon is a physical examination finding and thus neither ANA testing nor other laboratory work-up is useful for diagnosis.

Monitoring/prognosis. Twelve Grade “A” studies were identified that contained data regarding the sensitivity and/or specificity of the ANA to distinguish primary from secondary Raynaud’s phenomenon (Table 6 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (17,19,33,36,41,48,72–77). The overall sensitivity was 64% and specificity was only 41%. The positive and negative likelihood ratios were both very close to 1.0 (Table 2).

In another review on this area, 81% of patients with Raynaud’s phenomenon followed longitudinally never developed an associated systemic rheumatic disease, such as SLE, SSc, RA, or MCTD. A positive ANA test in patients with Raynaud’s phenomenon increases the risk of developing an associated systemic rheumatic disease from 19% to 30%, whereas a negative test reduced this risk to 7% (78).

Summary recommendations: Because no measures can be taken to prevent the development of systemic rheumatic diseases, patients presenting with Raynaud’s phenomenon should only undergo ANA testing if signs or symptoms of an underlying connective tissue disease are present.

Juvenile chronic arthritis. Diagnosis. Juvenile chronic arthritis (JCA) is primarily a clinical diagnosis made in children younger than 16 years of age. The nomenclature of juvenile chronic arthritis has changed recently with several subtypes being described. However, none of the literature we were able to find distinguished between the various subtypes of JCA.

Forty-one articles related to ANA testing to predict JCA were identified through the literature search. One was excluded because of nonrandom or nonconsecutive patient selection and 5 due to the absence of any clear reference standard. Of the remaining 35 studies, 21 were grade “A,” 4 were grade “B,” and 6 were grade “C” or “D.” Seven of the grade “A” studies used rodent substrate (mouse or rat) and the remaining 14 used HEp-2. All of the grade “A” studies were included in the analyses (Table 7 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (20,28,64,79–96). Studies included a variety of controls, such as children described as “not having arthritis,” as well as subjects with diseases other than arthritis and healthy controls. Considering these groups, the specificity of the ANA test for JCA was 39% and the sensitivity was 57% (Table 2). The likelihood ratio for a positive test was 0.95 and for a negative test 1.08.

Summary recommendations: ANA testing is not useful for diagnosing JCA and should not be performed as part of the routine diagnostic workup.

Monitoring/prognosis. The ANA plays an important role in stratifying the risk of uveitis in patients with JCA. The same 21 articles that were examined to determine the value of ANA testing for diagnosis of JCA were used to calculate the performance characteristics of the ANA for uveitis associated with JCA. The sensitivity of the ANA for uveitis was 80% and the specificity was 53%. The likelihood ratio for patients with a positive test is 1.7 and for patients with a negative test 0.4.

Summary recommendations: Although likelihood ratios for ANA testing in patients with JCA to determine the probability of uveitis are modest, this Committee recommends that all patients with known juvenile chronic arthritis should be ANA tested because the sequelae of uveities are so devastating, and the condition is responsive to treatment.

Rheumatoid arthritis. Diagnosis. Forty-one articles related to ANA testing in patients with rheumatoid arthritis (RA) were identified through the literature search. Five were excluded because of nonrandom or nonconsecutive patient selection and 7 due to the absence of any clear reference standard. Of the remaining 30 studies, 14 were grade “A,” 2 were grade “B,” and 14 were grade “C” or “D.” Eight of the grade “A” studies used rodent substrate (mouse or rat) and the remaining 6 used HEp-2. Only the grade “A” studies were included in these analyses (Table 8 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>.) (17,18,28,30,33,34,36,66,67,97–101).

The weighted average sensitivity of the ANA for RA was 41% and the specificity was 56% (Table 2). The likelihood ratio for patients with a positive test is 0.9 and for patients with a negative test 1.1.

Summary recommendations: Although positive ANA testing is not uncommon in patients with RA, the presence of the ANA has no diagnostic significance in RA, and ANA testing is not useful in patients suspected of having RA.

Monitoring/prognosis. There are no data to support or reject the use of the ANA for monitoring the activity of RA or for determining prognosis.

Drug-associated lupus erythematosus. Diagnosis. Some medications are known to be associated with a positive ANA and a lupus-like syndrome. No standard diagnostic criteria for drug-associated lupus erythematosus (drug LE) exist, but all studies of this condition use the presence of a positive ANA in the syndrome’s definition. Thus, it is impossible to determine the sensitivity or specificity of the ANA for drug LE. Studies of patients exposed to medications known to be associated with lupus reveal that many patients without lupus symptoms develop a positive ANA. The prognostic significance of this finding is unclear. However, similar to testing for SLE, the clinical significance of a positive ANA in a patient suspected of having drug LE can only be interpreted in the clinical context. A drug history should be sought in all patients who develop symptoms consistent with SLE to determine whether they have recently been exposed to any of the following medications: hydralazine, procainamide, isoniazid, chlorpromazine, quinidine, methyl dopa, minocycline, or any anti-convulsant (102–110).

Summary recommendations: Although the performance of the ANA in diagnosing patients with drug LE cannot be calculated, the Committee suggests that ANA testing should be pursued for patients with symptoms suggestive of SLE who are taking a drug associated with drug LE.

Monitoring/prognosis. There are no data to support the use of ANA testing for monitoring or prognosis regarding drug LE.

Table 10. Conditions associated with a positive antinuclear antibody (ANA)

ANA very useful for diagnosis
Systemic lupus erythematosus
Systemic sclerosis
ANA somewhat useful for diagnosis
Sjögren's syndrome
Polymyositis-dermatomyositis
ANA very useful for monitoring or prognosis
Juvenile chronic arthritis
Raynaud's phenomenon
ANA is a critical part of the diagnostic criteria
Drug-associated lupus
Mixed connective tissue disease
Autoimmune hepatitis
ANA not useful or has no proven value for diagnosis, monitoring or prognosis
Rheumatoid arthritis
Multiple sclerosis
Thyroid disease
Infectious disease
Idiopathic thrombocytopenic purpura
Fibromyalgia

Mixed connective tissue disease. *Diagnosis.* All diagnostic criteria for mixed connective tissue disease (MCTD) require a positive ANA (antibodies to extractable nuclear antigens are always associated with a positive ANA) and thus defining sensitivity or specificity is impossible. In patients suspected of having MCTD, a positive ANA should prompt testing for antibodies to RNP (111–114).

Summary recommendations: In patients suspected of having MCTD, ANA testing and appropriate testing for RNP must be performed to confirm this diagnosis.

Monitoring/prognosis. There are few data to support using the ANA for monitoring the activity of MCTD or for determining prognosis (115).

Autoimmune hepatitis. *Diagnosis.* A positive ANA has also been observed in patients diagnosed as having "autoimmune hepatitis." In addition to the absence of evidence of infection with known viral causes of hepatitis, the criteria by which autoimmune hepatitis is defined often include positive results on ANA and/or other autoantibody testing. Complicating the assessment of the prevalence of ANA in hepatic conditions has been the evolution in understanding of liver disease; for example, several studies addressing the prevalence of ANA in patients with hepatitis antedated the identification of hepatitis C. Therefore, definitions of disease states have changed over time.

From the literature search, 30 articles presenting data on ANA testing in patients with various forms of hepatitis were retrieved. Nine articles were rated as grade "C" or "D" and 16 as grade "B"; these were not considered further. Data from the 5 studies graded as "A" are shown in Table 9 (116–120) (Table 9 can be viewed in the online issue, which is available at <http://www.arthritisreres.org>). A positive test for ANA was frequently found in patients with liver disease. The studies examining patients with autoimmune hepatic disease noted a 63–91% prevalence of a positive ANA. However, because a positive ANA is

considered part of the definition of autoimmune hepatitis, this is circular.

Summary recommendation: A positive ANA is commonly seen in patients with diverse hepatic disease. It is included as part of the definition of "autoimmune hepatitis" but the presence of an ANA does not exclude other hepatic diseases.

Monitoring/prognosis. There are insufficient data to support using the ANA for monitoring the activity of autoimmune hepatitis or for determining prognosis. Data from 2 grade "A" studies suggested that the presence of an ANA does not affect the response to interferon therapy in hepatitis C infection (116,117).

Multiple sclerosis. *Diagnosis.* It has been reported that at least 25% of patients with multiple sclerosis (MS) will have a positive ANA. Literature review of the ANA in MS retrieved 8 articles, but only 3 were grades "A" or "B" (121–123). There are insufficient data to assess the utility of the ANA for diagnosis of MS. Perhaps of greater relevance to the clinician is the potential use of the ANA to differentiate MS from neuropsychiatric SLE. Again, there are not sufficient data to assess the value of the ANA for this purpose.

Monitoring/prognosis. There are insufficient data to determine the value of using the ANA for monitoring the activity of MS or for determining prognosis.

Idiopathic thrombocytopenic purpura. *Diagnosis.* Prior reports have noted that 10–40% of patients with idiopathic thrombocytopenic purpura (ITP) have a positive ANA and approximately 5% have SLE. The literature review retrieved 5 articles that addressed this issue; 2 were grade "A" and 1 grade "B" (124–126). This literature does not support any conclusions regarding the use of the ANA in differentiating ITP from SLE.

Monitoring/prognosis. There are insufficient data to determine the value of the ANA for monitoring the activity of ITP or for determining prognosis.

Autoimmune thyroid disease. *Diagnosis.* A variety of autoantibodies, including ANA, have been reported in the sera of patients with autoimmune thyroid disease. From the literature review, 5 articles were retrieved that specifically addressed this issue; 3 were grade "A" and 2 were grade "B" (127–131). The rates of positive ANA varied widely from 20–70% in these articles. The positive likelihood ratio of the ANA for autoimmune thyroid disease was 3.0 compared to healthy controls; however, a negative likelihood ratio could not be calculated.

Monitoring/prognosis. There are insufficient data to determine the value of the ANA for monitoring the activity of autoimmune thyroid disease or for determining prognosis.

Fibromyalgia. *Diagnosis.* It has been suggested that patients with fibromyalgia may have a positive ANA more frequently than controls. Eight articles were retrieved from the literature review; 2 were grade "A" and 2 were grade "B" (132–135). The prevalence of a positive ANA among patients with fibromyalgia ranged from 12–30%. There are

insufficient data to determine the value of an ANA in the diagnosis or the prognosis of fibromyalgia.

Other diseases. More than 50 articles were retrieved assessing the prevalence of a positive ANA in patients with various infectious diseases, malignancies, spondylarthropathies, and miscellaneous other conditions. For these conditions, there is a paucity of high quality data. Thus, we could not determine the value of ANA testing in these other diseases.

Conclusions

Positive antinuclear antibody testing is associated with a number of systemic rheumatic diseases as well as various other conditions (Table 10). The antinuclear antibody test has greatly assisted in the diagnosis of systemic lupus erythematosus and systemic sclerosis. However, the false positive rate associated with this test limits its usefulness as a screening test for rheumatic disease.

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