Learning Objectives

- Discuss the current trends in autoimmune connective tissue disease diagnosis by primary care providers, including risk assessment and the importance of early diagnosis
- Relate the clinical evidence for the association of biomarkers such as antinuclear antibody (ANA) presence and proper testing algorithms
- Demonstrate the ability to diagnose connective tissue diseases when ANA testing is negative
- Use and evaluate current biomarkers for diagnosis of early rheumatoid arthritis (RA)
- Identify the new types of biomarker testing available for diagnosing connective tissue diseases and explain how to interpret the tests

5

Overcoming Delays in Diagnosing Autoimmune Connective Tissue Diseases

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Senior Vice-Chair, Family Medicine & Community Health
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Autoimmune (AI) Disorders

- Affect up to 50 million people in the U.S.
- #2 cause of chronic illness
- Women are more likely to be affected than men
- Patients with one AI or AI in their family are at higher risk

80–100 types
- Rheumatoid arthritis
- Scleroderma
- Systemic lupus erythematosus
- Sjögren's syndrome
- Systemic sclerosis
- Mixed connective tissue disease
- Polymyositis
- Dermatomyositis

American Autoimmune Related Diseases Association (AARDA). Available at: https://www.aarda.org/news-information/statistics.

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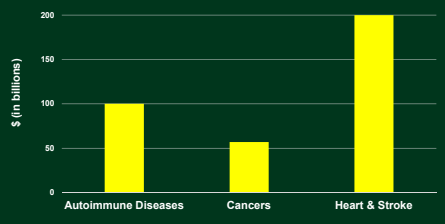
NIH Estimates Annual Direct Health Care Costs for AI Disorders to be in the Range of $100 Billion



American Autoimmune Related Diseases Association (AARDA). Available at: https://www.aarda.org/news-information/statistics.

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What You Do Matters!

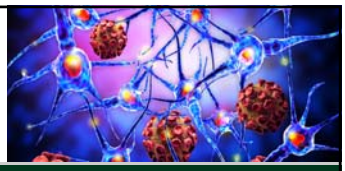
Diagnosis is often delayed (average 5 years)
- Delay in presentation to PCPs

Symptoms overlap/nonspecific (fatigue, joint and muscle pain, fever)
- Non-availability of one single diagnostic test
- Multiple tests combined with clinical findings are required to make a diagnosis

However, prompt diagnosis and treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other autoimmune CTDs will lead to improved long-term prognosis

Kumar K et al. *Rheumatology (Oxford).* 2007;46:1438-40. Raza K. *Rheumatology (Oxford).* 2010;49:406-10.

Clinical Signs and Symptoms of Autoimmune Connective Tissue Diseases



Common Diagnosis

Primary Raynaud's Phenomenon

- 5–10% U.S. women and 1–5% of men
- Purely vasospastic disease with pallor and cyanosis
  - Vessels return to normal caliber on recovery from cold challenge
- Should be bilateral – if unilateral consider proximal vascular stenosis/damage
- Does NOT ulcerate
- ANA negative (False + in 5%)

Garner R et al. *BMJ Open.* 2015;16:e006389. Maverakis E et al. *J Autoimmun.* 2014;48-49:60-5.

Primary vs Secondary Raynaud's Phenomenon

Primary
- At 2 years from onset, no other signs/sxs→ 50% chance primary
- At 5 years from onset, no other signs/sxs→ primary
- ANA (IFA) negative

Secondary
- Plus puffy hands (rings resized)
- Digital ulcers, pitting scars, loss of finger pad
- Sclerodactyly
- GERD, etc.
- ANA (IFA) positive

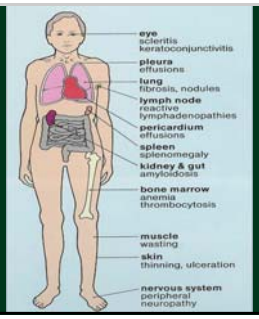
Carpentier PH et al. *J Vasc Surg.* 2006;44:1023-8.

Rheumatoid Arthritis (RA)

- Affects ~1.3 million Americans
  - Women are 2–3 x more likely to be diagnosed than men
  - Often develops between 35–50 years
- Symmetric, inflammatory, polyarthritis
- May cause deformity due to inflammation of tendons and ligaments and joint destruction via erosion of cartilage and bone
- In early disease, joint manifestations are often difficult to distinguish from other forms of inflammatory polyarthritis
- May have multiple extra-articular manifestations

American College of Rheumatology. Available at: https://www.rheumatology.org/portals/0/files/Rheumatic%20Diseases%20in%20America%20The%20Problem.%20The%20impact.%20The%20answers..pdf

RA: A Systemic Disease with Predilection for the Joints



Why Early Recognition of RA Is "Time Critical" – Window of Opportunity

- Without early diagnosis and treatment, RA will lead to:
  - Shortened survival
  - Significant disabilities
  - Joint damage

Handa R. Ch. 27. Available at: www.apiindia.org/pdf/medicine_update_2017/mu_037.pdf.

Evaluation for Suspected RA

- Thorough history, with attention to joint pain, stiffness, associated functional difficulties
- Complete exam to assess for synovitis, limited joint motion, extra-articular disease manifestations
- Bilateral radiographs of the hands, wrists, and feet
- Consider arthrocentesis
- Lab testing: ESR and CRP, RF, anti-CCP antibodies, and ANA

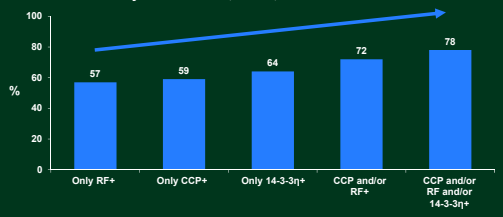
ANA=antinuclear antibodies; CCP=cyclic citrullinated peptide; CRP=C-reactive protein; ESR= erythrocyte sedimentation rate; RF=rheumatoid factor.

Venables PJW, Maini RN. UpToDate. Available at: https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis?search=Evaluation%20for%20Suspected%20RA&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

Potential for Combination Serological Assessment To Improve Diagnostic Utility in Early RA Detection

Early RA (n=99) vs healthy controls (n=189)

Sensitivity ratios for RF, ACPA, and RF and/or ACPA



ACPA=anti-citrullinated protein antibody. 14-3-3η = joint-derived proinflammatory mediator found in the synovial fluid and serum of patients with arthritis. Maksymowych WP et al. *J Rheumatol*. 2014;41:2104-13.

14-3-3η a Marker for RA Joint Damage

- A positive 14-3-3η test and higher titers at baseline indicate high joint damage progression risk 5 years out
- **Persistent negative 14-3-3η values show better outcomes**
  - A higher percentage of patients achieved SDAI remission based on a persistently negative test for 14-3-3η

SDAI=Simplified Disease Activity Index.
Carrier N et al. *Arthritis Res Ther*. 2016;18:37.
van Schaardenburg et al. American College of Rheumatology meeting. 2013;Abstract L13.

The 2010 ACR/EULAR Classification Criteria for RA

Joint involvement 1 large joint (0 points) 2–10 large joints (1 point) 1–3 small joints (2 points) 4–10 small joints (3 points) >10 joints [at least 1 small joint] (5 points)	**Duration of synovitis** <6 weeks (0 points) ≥6 weeks (1 point)
Serology RF/CCP negative (0 points) RF or CCP positive at low titer, <3 times ULN (2 points) RF or CCP positive at high titer, defined as >3 times ULN (3 points)	**Acute phase reactants** Normal ESR/CRP (0 points) Abnormal ESR/CRP (1 point)

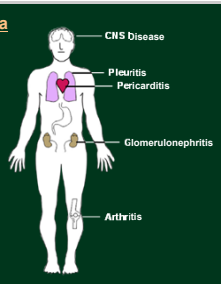
A score ≥6 points is required for classification as definite RA
Classification criteria ≠ diagnostic criteria
Therefore, some RA patients may not fulfill the classification criteria early, ie, at onset of disease

Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, 2nd through 5th metatarsophalangeal joints, thumb interphalangeal joints, and wrists. ULN=upper limit of normal. Aletaha D et al. *Ann Rheum Dis* 2010;69:1580-8.

Systemic Lupus Erythematosus (SLE)

Physical findings
- Lupus rash has the highest sensitivity for SLE (65%)

Immunologic Criteria
1. Antinuclear antibody
2. Anti-dsDNA
3. Anti-Sm
4. Anticardiolipin
5. Decreased complements
6. Direct Coomb's test



Lab findings
- ANA has the highest sensitivity for SLE (96.5%)

Roberson JM, James JA. *Rheum Dis Clin North Am*. 2014;40:621-35. Petri M et al. *Arthritis Rheum*. 2012;64:2677-86.

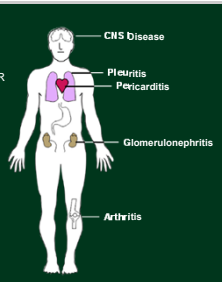
SLE Classification Criteria

Clinical Criteria

1. Acute Lupus Rash
2. Chronic Lupus Rash
3. Oral Ulcer
4. Alopecia
5. Arthritis
6. Serositis
7. Renal Disorder
8. Neurologic Disorder
9. Hemolytic Anemia
10. Leukopenia/Lymphopenia
11. Thrombocytopenia

SLICC Revised Criteria

1. Must meet 4 criteria
2. Must have:
   - At least 1 clinical and 1 immunologic criteria OR
   - Biopsy-proven lupus nephritis with anti-dsDNA or ANA



SLICC=Systemic Lupus International Collaborating Clinics.
Roberson JM, James JA. *Rheum Dis Clin North Am.* 2014;40:621-35. Petri M et al. *Arthritis Rheum.* 2012;64:2677-86.

Autoantibodies in SLE Diagnosis and Classification

Autoantibody test	Sensitivity estimate	Specificity for SLE?	Other diseases
ANA (HEp-2 IFLU)	98	No	Many
Anti-dsDNA	50	Yes (95%)	-
Anti-Histone	50	No	DIL, SSc, JIA
Anti-C1q	30	No	IC vasculitides[a]
Anti-Sm	10	Yes (99%)	-
Anti-Ro60	40	No	Sjögren's, CLE[a], SSc
Anti-SS-B/La	20	No	Sjögren's
Anti-U1RNP	20	No	MCTD
Rheumatoid factors	20	No	RA, Sjögren's
Anti-Cardiolipin IgG	20	No	Primary APS[a]
Anti-Cardiolipin IgM	10	No	Primary APS[a]
Lupus anticoagulant	10	No	Primary APS[a]

[a]The differential diagnoses can also be part of the SLE spectrum. APS=anti-phospholipid (Hughes') syndrome; CLE=cutaneous lupus erythematosus; DIL=drug-induced lupus; IC=immune complex; IFLU=immunofluorescence; JIA=juvenile idiopathic arthritis; MCTD=mixed connective tissue disease; RA=rheumatoid arthritis; SSc=systemic sclerosis. Aringer M et al. *Lupus.* 2016;25:805-11.

Mixed Connective Tissue Disease (MCTD)

- 80% are women aged 5 to 80, often peaking in adolescence/early 20s
- Raynaud's phenomenon, joint pains, skin abnormalities, muscle weakness
  - First manifestations resemble early SLE, SSc, polymyositis, or even RA
  - Diffuse swelling of the hands is typical
  - Almost all patients have polyarthralgias; 75% have frank arthritis
- Absence of severe renal and CNS disease is a hallmark of MCTD
- Test for ANA, U1RNP, anti-Sm, and anti-DNA
  - Speckled ANA in high titer
  - High titer to U1RNP is common; anti-Sm and anti-DNA are absent
  - RF frequently present with high titer

Hajj-ali RA. Merck Manual. Available at: www.merckmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/autoimmune-rheumatic-disorders/mixed-connective-tissue-disease-mctd

Biomarker Testing for Autoimmune Disorders – What You Need To Know

Conditions Associated with a Positive Antinuclear Antibody (ANA) Test

Condition	Sensitivity %	Specificity %
Systemic lupus erythematosus	93 – 95	57
Sjögren's syndrome	48	52
Systemic sclerosis	85	54
Juvenile idiopathic arthritis	57	39
Juvenile idiopathic arthritis with uveitis	80	53
Rheumatoid arthritis	41 – 86	56
Polymyositis/dermatomyositis	61	63
Drug-induced lupus*	NA	NA
Mixed connective tissue disease*	NA	NA

*For drug-induced lupus and mixed connective tissue disease, the diagnostic criteria require a positive ANA, therefore specificity and sensitivity cannot be determined.
Scholz J et al. *Clin Chem Lab Med.* 2015;53:1991-2002. Colglazier CL, Sulej PG. *South Med J.* 2005;98:185-91.

ANA IFA vs ANA ELISA: Which Lab Test?

ANA IFA

- Still considered the gold standard by ACR
- Higher titers are generally associated with greater likelihood of CTD disease, but do not reflect disease activity
- When positive, results reported as a titer with a particular type of immunofluorescence pattern
- Different patterns are associated with a variety of autoimmune disorders
- Automated tiered testing possible when positive results obtained

ANA ELISA

- More economical
- Allows for large volume of testing
- Less labor-intensive
- Tests for only several biomarkers at a time
- Reports a number for positivity
- Reliability and accuracy system-dependent
- Results in comparison with IFA variable

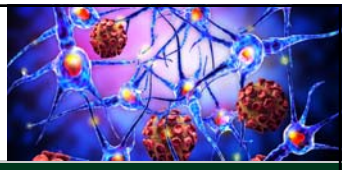
ELISA=enzyme-linked immunosorbent assay; IFA=immunofluorescence.
Meroni PL, Schur PH. *Ann Rheum Dis.* 2010 Aug; 69:1420-2. Mahler M et al. *Immunopharmacol Immunotoxicol.* 2016;38:14-20.

ACR Position Statement: Methodologies of Testing for Antinuclear Antibodies

- Supports the immunofluorescence (IF) antinuclear antibody (ANA) test using Human Epithelial type 2 (HEp-2) substrate as the gold standard for ANA testing.
- Laboratories should specify the methods utilized for detecting ANAs.
- Laboratories using alternative multiplex platforms or other assays for detecting ANAs must provide requested data that the alternative assay has the same or improved sensitivity compared to IF ANA.
- In-house assays for detecting ANA as well as anti-DNA, anti-Sm, anti-RNP, anti-Ro/SS-A, anti-La/SS-B, etc., should be standardized according to national (eg, CDC) and/or international (eg, WHO, IUIS) standards.

American College of Rheumatology. https://www.rheumatology.org/Practice-Quality/Administrative.../Position-Statements

ANA IFA



Interpretation

ANA by Immunofluorescence Antibody: Reporting Titer and Pattern

- ANA titers:
  - <1:40 negative
  - 1:40–1:80 low antibody level
  - >1:80 elevated antibody level
- Any titer above 1:40 along with pattern interpretations is reported
- Patterns aid in differential diagnosis

Pattern	Picture	Antibody	Disease State(s)
Rimmed/ peripheral		Anti-DNA	SLE
Homogenous		Anti-DNA Anti-histone	RA & SLE Misc. Disorders
Speckled		Anti-Sm & RNP Anti-Ro & La Anti-Jo-1 & Mi-2 Anti-Scl-70	SLE & SSc PM/DM
Centromere		Anti-centromere	lcSSc (formerly CREST)
Nucleolar		Anti-nucleolar	SLE & SSc

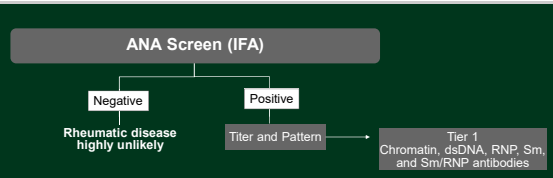
lcSSc=limited cutaneous of systemic sclerosis.

ANA IFA: Testing Subserologies when ANA is Positive

A *reflex to titer and pattern* approach to testing may be used to identify autoimmune (AI) disorders when ANA is **positive**

After Positive ANA	Antibodies tested	Potential Diagnosis when Positive
Tier 1	Chromatin, dsDNA, RNP, Sm, and Sm/RNP	SLE, MCTD
Tier 2	Jo-1, Scl-70, SS-A, and SS-B	Sjögren's Syndrome, Systemic Scleroderma, Polymyocitis
Tier 3	Centromere B and ribosomal P	Limited SSc Syndrome, Neurologic SLE

ANA IFA: Subserologies (cont.)



RNP=ribonucleoprotein.

ANA IFA: Subserologies (cont.)

Tier 1
Chromatin, dsDNA, RNP, Sm, and Sm/RNP antibodies

Negative

Tier 2
Jo-1, Scl-70, SS-A, and SS-B antibodies

Positive

Antibody Test	Systemic Lupus Erythematosus	Mixed Connective Tissue Disease
dsDNA	+ (high specificity)	–
Chromatin	+ (high specificity)	–
Sm	+ (high specificity)	–
Sm/RNP	+	+ (high titer)
RNP	+	+ (high titer)

ANA IFA: Subserologies (cont.)

Tier 2
Jo-1, Scl-70, SS-A, and SS-B antibodies

Negative

Tier 3
Centromere B and ribosomal P antibodies

Positive

Antibody Test	Sjögren's Syndrome	Systemic Scleroderma	Polymyositis
SS-A	+	–	–
SS-B	+	–	–
Scl-70	–	+	–
Jo-1	–	–	+

ANA IFA: Subserologies (cont.)

Tier 3
Centromere B and ribosomal P antibodies

Negative

No evidence of rheumatic disease shown by analytes tested

Positive

Antibody Test	Limited SSc Syndrome	Neurologic SLE
Centromere	+	–
Ribosomal P	–	+

ACR *Choosing Wisely* Recommendation When Considering ANA Testing

American College of Rheumatology

Don't test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease

- Tests for anti-nuclear antibody (ANA) sub-serologies (including antibodies to dsDNA, Smith, RNP, SS-A, SS-B, Scl-70, centromere) are usually negative if the ANA is negative
- Broad testing of autoantibodies should be avoided; instead the choice of autoantibodies should be guided by the specific disease under consideration

Exceptions include anti-Jo1, which can be positive in some forms of myositis, or occasionally, anti-SS-A, in the setting of lupus or Sjögren's syndrome

ACR. Available at: http://www.choosingwisely.org/societies/american-college-of-rheumatology

When to Refer to a Rheumatologist…

- Unclear/confirm diagnosis
- Treatment assistance
- Other inflammatory/musculoskeletal conditions
  - Complex regional pain syndrome
  - Serum sickness
  - Vasculitis
  - Osteoarthritis/Metabolic bone disease
  - Fibromyalgia
  - Sarcoidosis

American College of Rheumatology Referral Guidelines, August, 2015. Available at: https://www.rheumatology.org/Portals/0/Files/Referral%20Guidelines.pdf

Diagnosing Autoimmune CTDs

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Sjögren's Syndrome Is Most Common in Patients with RA and in SLE and SSc

Clinical presentation

- Most patients are women, and onset is usually at age 40–60 years
- **Sicca symptoms: Xerophthalmia (dry eyes) and xerostomia (dry mouth)**
- Bilateral parotid swelling
- Systemic extraglandular manifestations: arthritis/arthralgias, lung, kidney, liver, and skin
- Associated with lymphoma

Lab test results may indicate the following

- Elevated erythrocyte sedimentation rate (ESR)
- Anemia
- Leukopenia
- Eosinophilia
- Hypergammaglobulinemia
- Presence of antinuclear antibodies, especially anti-Ro and anti-La
- Presence of rheumatoid factor (RF)
- Diminished creatinine clearance (~50% of patients)

SSc=systemic sclerosis. Rischmueller M et al. *Best Pract Res Clin Rheumatol*. 2016;30:189-220.
Ramos-Casals M et al, ed. *Sjögren's Syndrome: Diagnosis and Therapeutics*. 1st ed. Springer-Verlag London. 2012

2016 ACR-EULAR Diagnostic Criteria for Primary Sjögren's Syndrome

Criteria

• Autoantibody detection: anti-SS-A (Ro)	3 pt
• Histology —Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥1	3 pt
• Unstimulated salivary flow rate ≤0.1 mL/min	1 pt
• Schirmer ≤5 mm/5min on at least one eye	1 pt
• Ocular staining score ≥5	1 pt

Diagnosis

Score ≥4 points, after application of

- Inclusion criteria:
  - Dryness of eyes and/or mouth for at least 3 months, not explained otherwise
- Exclusion criteria:
  - Status post head/neck radiation
  - HIV/Aids
  - Sarcoidosis
  - Active infection with hepatitis C virus
  - Amyloidosis
  - Graft versus host disease
  - IgG4-related disease

The lack of any other potentially associated disease is the key requirement

Shiboski CH et al. *Arthritis Rheumatol*. 2017;69:35-45.

Testing for Sjögren's Syndrome

Diagnostic

- Positive ANA (Titer ≥1:320)
  - Pattern=Speckled
- SS-A (Ro)
  - May have significance in patients who are ANA negative. Additional monitoring to be considered.
- SS-B (La)
  - Probably does not have significance in patients who are ANA negative
- Rheumatoid factor can be positive

Confirmatory

- Lip biopsy
- Ocular staining for integrity of tear film

Testing for Systemic Lupus Erythematosus (SLE)

Diagnostic

- ANA is reported to be "**positive**"
  - Titer = 1:320
  - Pattern = Homogeneous or speckled
- Specific antibodies-SS-A/SS-B; Smith (Sm); anti-DNA (dsDNA); anti-chromatin
- Antiphospholipid antibody positivity
- Complement levels (C3/C4/CH50)
- Complete blood count with differential & platelets
- Creatinine & urinalysis
- Erythrocyte sedimentation rate/C-reactive protein (ESR/CRP)

Disease Activity

- Anti-native DNA antibody (anti-dsDNA)
- C3/C4
- (CBC w/ diff & platelets)
- Creatinine
- ESR/CRP
- Urinalysis

ANA: Once this is positive, there is no need to repeat

Continue to treat or refer to Rheumatologist

Systemic Sclerosis (SSc)

Epidemiology

- Peak age range: 35–64
  - Younger age in women and with diffuse disease
- Female:Male = 3:1
  - 8:1 in child-bearing years
- Incidence: 20 cases/million/year in U.S.
- Prevalence: 240 cases/million in U.S.

Etiology

- Unknown
- Environmental Exposures
  - Silica exposure in men conferred increased risk
  - Silicone breast implants: No definite risk identified
  - Vinyl chloride exposure increased risk of SSc-like disorder: Eosinophilic Fasciitis
  - Bleomycin
  - L-tryptophan: Eosinophilia-Myalgia Syndrome

Barnes J, Mayes MD. *Curr Opin Rheumatol*. 2012;24:165-70.

2013 ACR/EULAR Classification Criteria for Systemic Sclerosis (SSc)

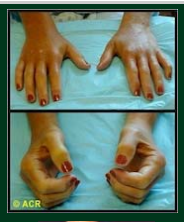
Items	Sub-Items	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (only count the highest score)	Puffy fingers Whole finger, distal to MCP	2 4
Fingertip lesions (only count the highest score)	Digital tip ulcers Pitting scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease		2
Raynaud's phenomenon		3
SSc-related autoantibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3

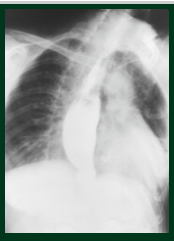
Score of 9 or more = Definite SSc

van den Hoogen F et al. *Arthritis Rheum*. 2013;65:2737-47. *Ann Rheum Dis*. 2013;72:1747-55.

Systemic Sclerosis: Organ Involvement

- Skin
- Lung
- GI Tract
- Heart
- Kidneys
- Muscle





Steen VD, Medsger TA Jr. *Arthritis Rheum*. 2000;43:2437-44.

Systemic Sclerosis – Diffuse Cutaneous

- Skin tightness proximal to elbows or knees often with truncal involvement
- "Salt and pepper" pigment changes
- Pulmonary fibrosis
  - Secondary pulmonary artery hypertension
- Renal/hypertensive crisis
- Raynaud's phenomenon
- GERD

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Systemic Sclerosis – Limited Cutaneous

- Skin tightness distal to elbows or knees; no truncal involvement
- Raynaud's phenomenon
- Digital ulcers
- Pulmonary arterial hypertension (as a late complication)
- GERD

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Testing for Systemic Sclerosis

- Serologic
- ANA positive
  - Titer=1:320
  - Pattern=Speckled, nucleolar, or centromere
- Anti-centromere antibody
  - Limited cutaneous systemic sclerosis (formerly CREST)
  - Associated with higher risk of pulmonary hypertension
- Anti-nucleolar antibody
  - Diffuse cutaneous systemic sclerosis (formerly PSS)
- Anti-Scl-70 (Topoisomerase I)
  - Suggests high risk of pulmonary involvement with fibrosis
- RNA polymerase 3
  - Associated with higher risk of developing diffuse cutaneous disease, renal crisis, and a temporal relationship to malignancy

Continue to treat or refer to Rheumatologist or refer to Scleroderma Center

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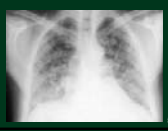
Idiopathic Inflammatory Myopathies (IIM)

- Definition: Absence of an associated autoimmune CTD – so **not** with features of MCTD, SLE, or scleroderma
- Dermatomyositis - with typical skin rash; Polymyositis without typical skin rash
- Proximal muscle weakness in shoulder/hip areas
  - ↓ Ability to get something from/lift something to a high shelf, comb hair, climb stairs, etc.
- Frequently painless or with minimal muscle soreness
- Complications
  - Difficulty swallowing – weakness of the oropharyngeal muscles
  - Difficulty breathing – respiratory muscle weakness
  - Associated interstitial lung disease
  - Calcinosis particularly in childhood cases



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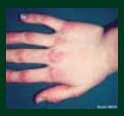
Dermatomyositis Signs

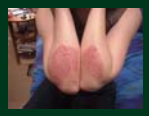
Heliotrope = pink purple color, named after the plant heliotropium peruvianum

Heliotrope rash with swelling

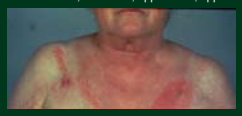
Gottron's Papules



Gottron's Sign



Poikilodermatous macules in a "Shawl" distribution over anterior chest, shoulders, upper arms, upper back



Koler RA, Montemarano A. *Am Fam Physician*. 2001;64:1565-72. Babcock SM et al. *Can J Gen Int Med*. 2013;8:28-30. ACR. High Impact Rheumatology. www.rheumatology.org

Dermatomyositis (DM) and Polymyositis (PM)

EULAR/ACR Classification Criteria for Idiopathic Inflammatory Myopathies (IIM)

- Patients with pathognomonic skin rashes (heliotrope rash, Gottron's papules, and/or Gottron's sign) of DM are accurately classified without including muscle biopsy
- For patients without these skin manifestations, muscle biopsy is recommended
- For DM patients without muscle involvement, a skin biopsy is recommended
- Classification criteria provide a score & corresponding probability of having IIM

Performance	Without muscle biopsy	With muscle biopsy
Sensitivity, mean (95% CI) %	87 (84-90)	93 (89-95)
Specificity, mean (95% CI) %	82 (77-87)	88 (83-93)

Lundberg IE et al. *Arthritis Rheumatol* 2017;69:2271-82.

Rheumatic Diseases to Consider when ANA Test is Negative

- Ankylosing spondylitis
- Autoimmune thyroid disease
- Rheumatoid arthritis
- Inflammatory bowel disease
- Multiple sclerosis
- Myasthenia gravis
- Occasionally Sjögren's syndrome (when SS-A and SS-B are cytoplasmic rather than nuclear)
- Autoimmune neuropathies and vasculitis
- Celiac disease and bullous disease
- Gout / pseudogout
- Idiopathic myositis / polymyositis (not associated with MCTD)

Diagnosis of Diseases beyond ANA Test

When ANA is positive, but specific antibodies tested negative from ANA IFA with reflex for rheumatic diseases cascade

- Rheumatoid arthritis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Autoimmune thyroid disease
- Addison's disease
- Pernicious anemia

Drugs Implicated in the Development of Drug-induced SLE

Definite	Probable	Possible	Case Reports
Hydralazine Procainamide Isoniazid Methyldopa Quinidine Minocycline Chlorpromazine	Sulfasalazine Antithyroid Anticonvulsants Ethosuximide, Phenytoin Primidone, Valproate Zonisamide, Carbamazepine Statins Lovastatin, Simvastatin Fluvastatin, Pravastatin Atorvastatin Terbinafine Penicillamine Fluorouracil agents Hydrochlorothiazide	Antibiotics Ciprofloxacin Penicillin Tetracycline Nitrofurantoin Cefepime Cefuroxime NSAIDS Ibuprofen Diclofenac Miscellaneous Lithium Interferons Gold salts	Infliximab Etanercept Interleukin-2 Zafirlukast Clobazam Tocainide Lisinopril Bupropion

Cessation of offending therapy offers the best outcome

Garza A. Pharmacy Times. Available at: http://www.pharmacytimes.com/publications/issue/2016/january2016/drug-induced-autoimmune-diseases?p=1.
Vasoo S. *Lupus*. 2006;15:757-61. Araújo-Fernández S et al. *Lupus*. 2014; 23:545-53.

Summary

- ANA testing can lead to early diagnosis & treatment of potentially devastating diseases
- ANAs are a family of diagnostic antibodies that may have clinical significance
  - A highly sensitive but not specific test
- ANA should be ordered in conjunction with clinical presentation or other laboratory findings suggestive of rheumatologic disease
- ANA IFA is the American College of Rheumatology gold standard for testing
- Initial ANA IFA testing should be followed with clinically appropriate subserologic testing only if ANA IFA titer is elevated

Cases for Review

Courtesy of Maureen D. Mayes, MD, MPH

Robert Baldor, MD
Maureen Mayes, MD

Ms. Smith: 55-year-old woman

Chief complaint: Joint pain, swelling, stiffness in hands and wrists

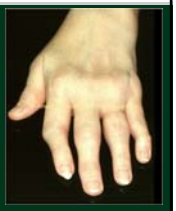
- 2–3 month history of gradually worsening joint pain with swelling of hands and wrists
- Joint stiffness worse in the morning and lasts for 30–60 minutes, improved with acivity and hot shower
- Improved minimally with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) but symptoms recur in a few hours
- Reduced grip strength – difficulty opening jars and keyboarding
- Review of systems is otherwise negative

Ms. Smith: 55-year-old woman

- Medical history
  - Type 2 diabetes diagnosed 3 years ago
    - Improved with diet and weight loss
  - Pregnancy history: 2 children, no miscarriages
- Family history
  - Grandmother had "rheumatism" in her hands & mother developed "joint problems" in her 40s
  - Father died of MI at early age
- Social history
  - Tobacco: 25 pack years (1 pack per day for 25 years, quit 2 years ago)
  - Alcohol: 2–3 drinks per week
  - Occupation: Clerical work but finding it difficult to perform keyboarding

Ms. Smith: 55-year-old woman

Physical exam



- Bilateral swelling of PIP, MCP joints, and wrists
- Joints are tender to palpation
- DIP joints are neither tender nor swollen
- Grip strength is decreased and fist formation is incomplete
  - Can just touch fingertips to palms but cannot bury her nails
- Palmar erythema is present
  - No other skin rashes
- No nail pitting or bruises noted

Ms. Smith: 55-year-old woman

Results of "routine" labs: CBC, LFT, urinalysis, inflammatory markers:

- CBC: Normocytic anemia, mild thrombocytosis, normal WBC
- LFT: Normal
- Urinalysis: Unremarkable
- ESR: 35 mm/hr
- CRP: 5 mg/dL (normal <3.0 mg/dL)

CBC=complete blood count; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; LFT=liver function test; WBC=white blood count.

Ms. Jones: 24-year-old woman

Chief complaint: Joint pain, swelling, and stiffness in hands and wrists

- 2–3 month history of gradually worsening joint pain with swelling of hands and wrists
- Joint stiffness worse in the morning and lasts for 30–60 minutes, improved with activity and hot shower
- Improved minimally with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) but symptoms recur in a few hours
- Reduced grip strength – difficulty opening jars and keyboarding
- Review of systems is otherwise negative

Ms. Jones: 24-year-old woman

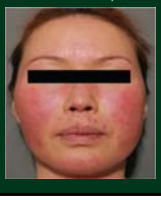
- Medical/surgical history:
  - None (note: never pregnant)
- Family history
  - Mother with “overactive” thyroid disease treated medically
- Social history:
  - Alcohol: ~2–3 drinks per month
  - Tobacco: None/never
  - Illicit drugs: Denies
  - Caffeine: 2–3 cups of coffee per day
  - Occupation: Graduate student

Ms. Jones: 24-year-old woman

Physical exam

- Joints: Mild synovial thickening of wrists only, with tenderness to palpation of wrists, MCPs, PIPs
- Skin: Raised erythema over cheeks, sparing the naso-labial folds; rash in the V-area of the chest
- HEENT: + painless oral ulcer
- Extremities: Trace pedal edema

Otherwise – exam is normal



Ms. Jones: 24-year-old woman

Routine labs with inflammatory markers:

- CBC: Mild normocytic anemia, modest leukopenia
- CMP: Albumin 3.0 (LLN = 3.5); otherwise normal
- Urinalysis: + 2 proteinuria
- ESR: 35 mm/hr (ULN = 20)
- CRP: 5 mg/dL (normal <3.0 mg/dL)

Mr. Williams: 50-year-old man

Chief complaint: Diffuse hand swelling, stiffness and decreased flexibility

History of present illness:

- At least 4 months of stiff and diffusely swollen fingers
- Frequent episodes on 5–10 min cold exposure where fingers on both hands become numb and lose color, turning white or even purple
- New onset of frequent heartburn after dinner
- Trouble going up a flight of stairs due to “feeling winded”

Mr. Williams: 50-year-old man

- Medical history
  - Hypertension (diagnosed 5 years ago); resolved with weight loss/diet change
- Family history
  - Father: Stroke at age 77, died 1 year later
- Social history
  - Tobacco: None/never
  - Alcohol: A few beers on the weekend
  - Illicit Drugs: Denies
  - Occupation: Warehouse worker x25 yrs
- Medications
  - None

Mr. Williams: 50-year-old man

Physical exam

- Skin thickening of hands (2+), forearms (1+) , upper arms (1+) and face (1+)
- Decreased range of motion of fingers and wrists related to overlying skin thickening
- Diffuse hand swelling
- Hyperpigmentation in hands and arms
- Few rales in bases bilaterally
- Physical exam is otherwise normal

Mr. Williams: 50-year-old man

Results of routine laboratory tests:

- CBC: Normocytic anemia (mild)
- CMP: WNL (normal liver and kidney function tests)
- TSH: 2.0 mIU/L
- Urinalysis: Unremarkable

CBC=complete blood count; CMP=comprehensive metabolic panel; TSH=thyroid-stimulating hormone.

Mr. Williams: 50-year-old man

Results of autoimmune antibodies tests:

- ANA IFA: 1:640 nucleolar & speckled patterns
- CK: 122 U/L (ULN = 200)
- anti-Scl-70: Positive >8 (ULN <1.0)
- anti-centromere: Negative
- anti-RNA Polymerase III: Negative