Systemic Lupus Erythematosus

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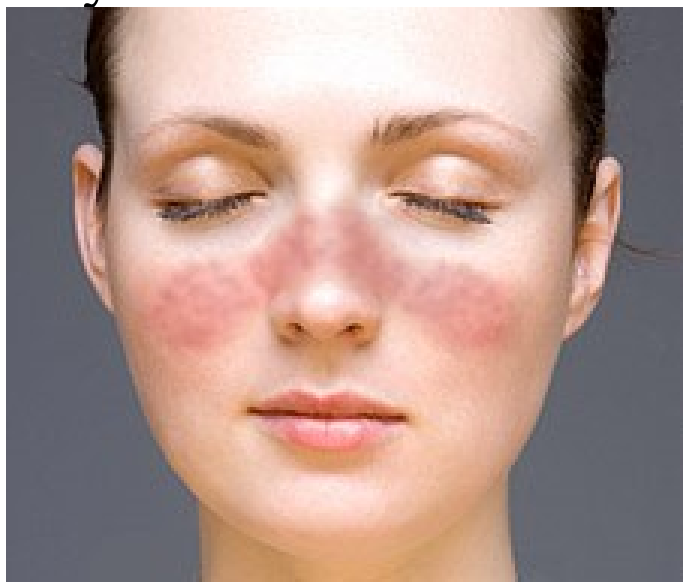
SLE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies resulting from the dysfunction of T cells, B cells, and dendritic cells. These antibodies are principally anti-nuclear and induce an inflammatory response throughout the body.

CASE 1

A 25 year old female presents with fatigue, arthralgias, and a rash. She reports that she has been having joint pain with worsened stiffness and swelling in the mornings for the past three months. She has also noted rashes, particularly on her face and neck, over this same time period.



On exam, several MCPs are tender to palpation with trace synovitis, and she has multiple well-demarcated erythematous plaques on her face and neck with fine overlying scale.

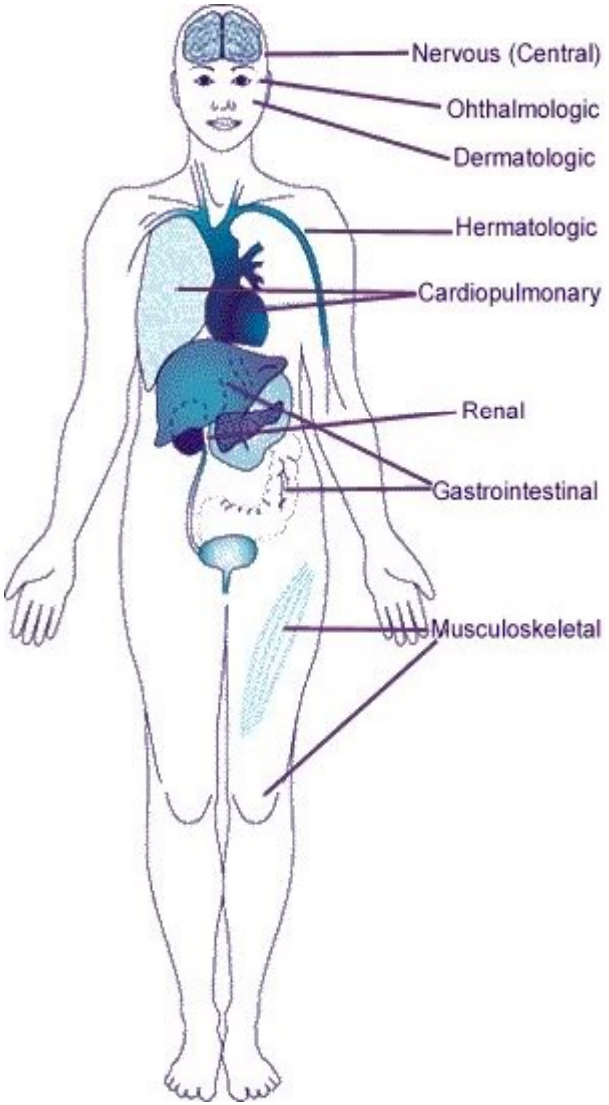
Basic labs : total lymphocyte count of 500 (normal Lymphocytes: 1.5–3.5 x 10^9/L) , a creatinine of 1.6, and red blood cell casts and 3+ proteinuria on urinalysis. A 24-hour urine protein returns at 4.2 grams/day.

Autoantibody testing :positive ANA at a titer of 1:640 with a diffuse homogeneous staining pattern, the presence of high titer double stranded DNA antibodies, the presence of anti-Smith antibodies, and hypocomplementemia.

SLE Around the World

- 5 million people with SLE
  - 40-80 of every 100,000
- 90% of cases occur in women
  - 10X more susceptible
- Contributions from ethnicity
  - Incidence compared to Caucasians
    - 3X higher for Asians
    - 4X higher for African Americans (women)
  - Mortality compared to Caucasians
    - 2X higher for Asians
    - 3X higher for African Americans (women)
- Survival Rates
  - ~90-95% in Western world

Multi-Systemic Autoimmune Disease

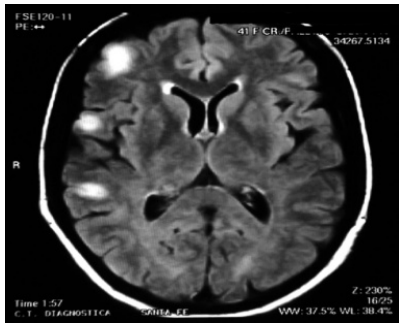


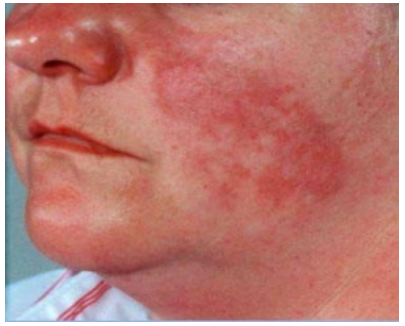
The spectrum of autoimmune disease

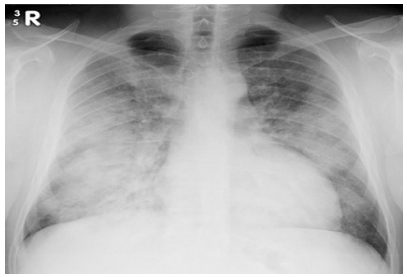
Organ Specific Autoimmune Diseases

♦ Graves Disease	(Thyroid: TSHR Abs, TPO Abs)
♦ Hashimoto Thytreoiditis	(Thyroid: TPO Abs, Tg Abs)
♦ Diabetes Type I	(Pankreas: GAD II Abs, IA2 Abs, ICA)
♦ Goodpasture Syndrome	(Kidney: GBM Abs)
♦ Pernicious Anemia	(Stomach: Parietal Cell Abs)
♦ Primary Biliary Cirrhosis	(Liver, Bile: AMAbs)
♦ Myasthenia Gravis	(Muscles: AChR Abs)
♦ Dermato-/Polymyositis	(Skin / Muscles: Jo 1 Abs)
♦ Vasculitis	(Vessels: ANCA)
♦ Rheumatoid Arthritis	(Joints: CRP, RF, RA33 Abs, Sa Abs)
♦ MCTD	(RNP Abs)
♦ Scleroderma	(Scl 70 Abs, CENP Abs, PM/Scl Abs)
♦ SLE	(ANA, Cardiolipin Abs, Beta 2 GP I Abs)

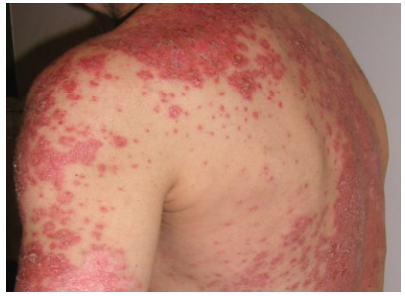
Multi-systemic Autoimmune Diseases

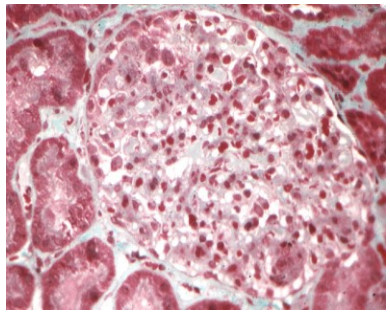


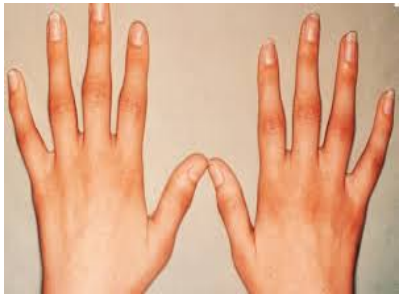




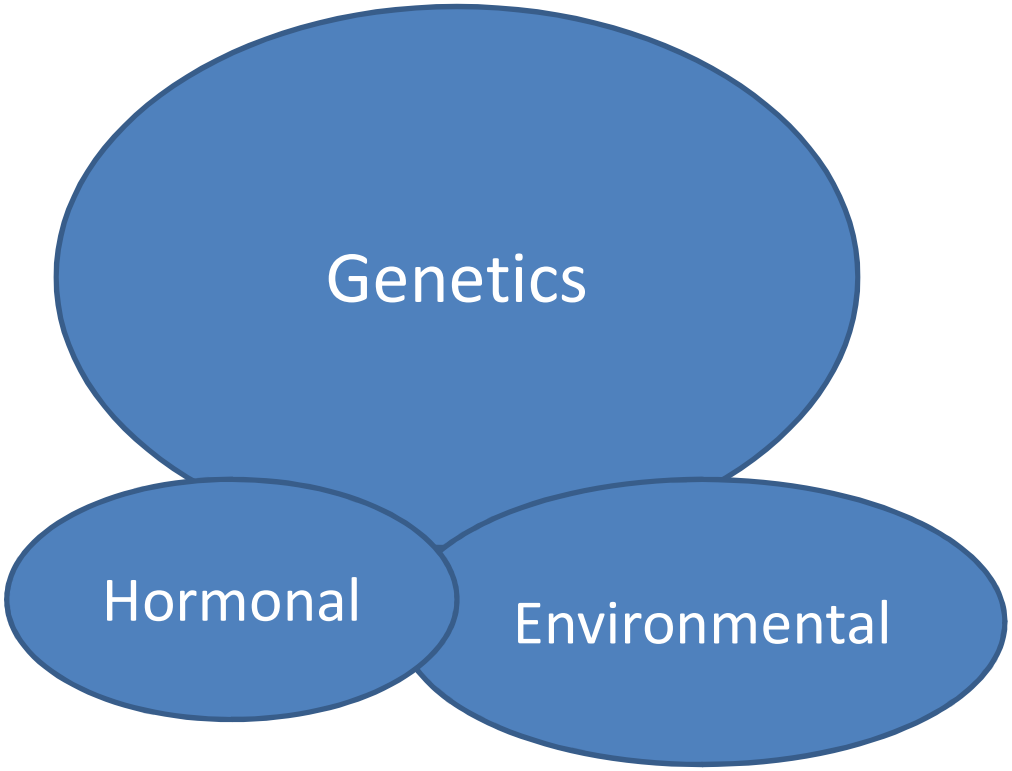
SLE is a heterogeneous disease







Aetiology ?



Environmental

- Ultraviolet light
- Drugs
- Infections(EBV)
- Smoking
- Silica dust

Genetic Predispositions

- First degree relatives of patients with SLE have a higher prevalence of autoantibodies and a higher risk of SLE and other autoimmune diseases

- Some of the first degree relatives of patients with SLE develop SLE-specific autoantibodies but never develop clinical disease

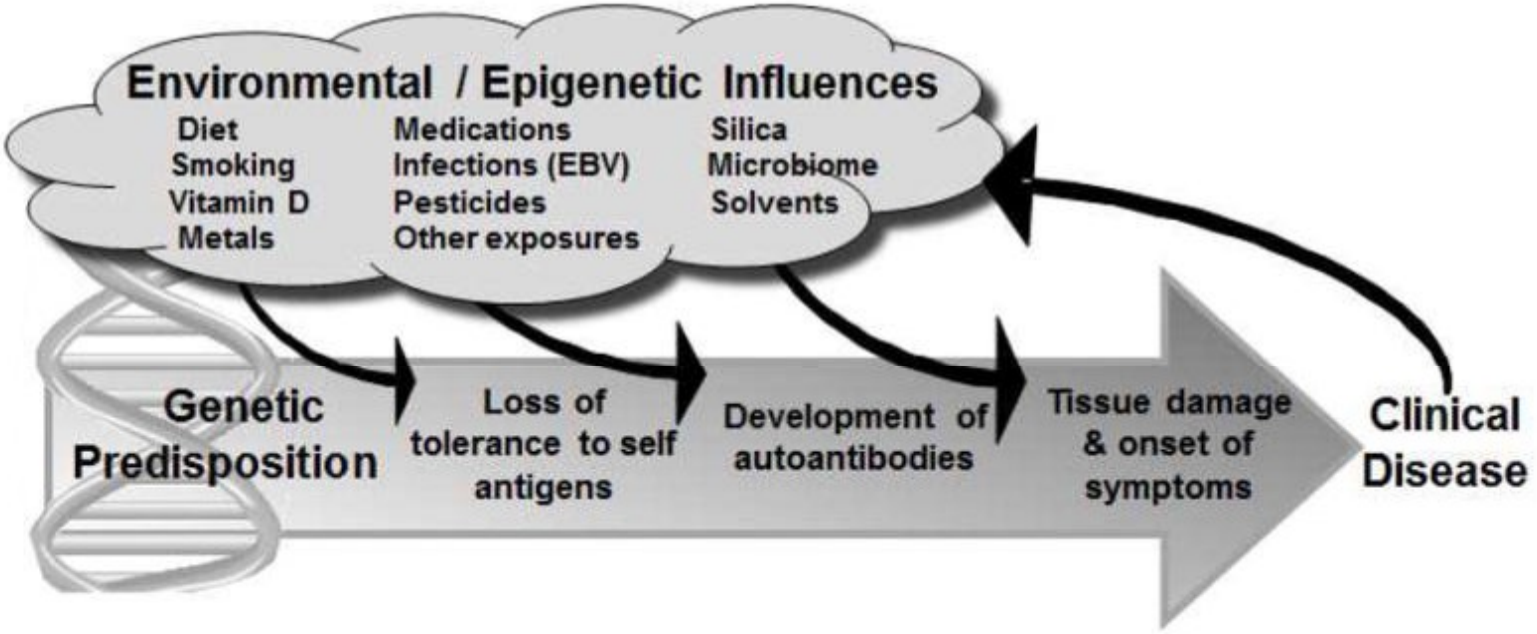
Genetic Predispositions

- HLA genes most studied
  - HLA Class II gene polymorphisms
  - HLA DR2 and DR3

- **Klinefelter Syndrome**
  - XXY is found in excess among men with SLE.
  - Men commonly have SLE that is more severe than that found among women, but the 47,XXY men had less severe SLE than other men.

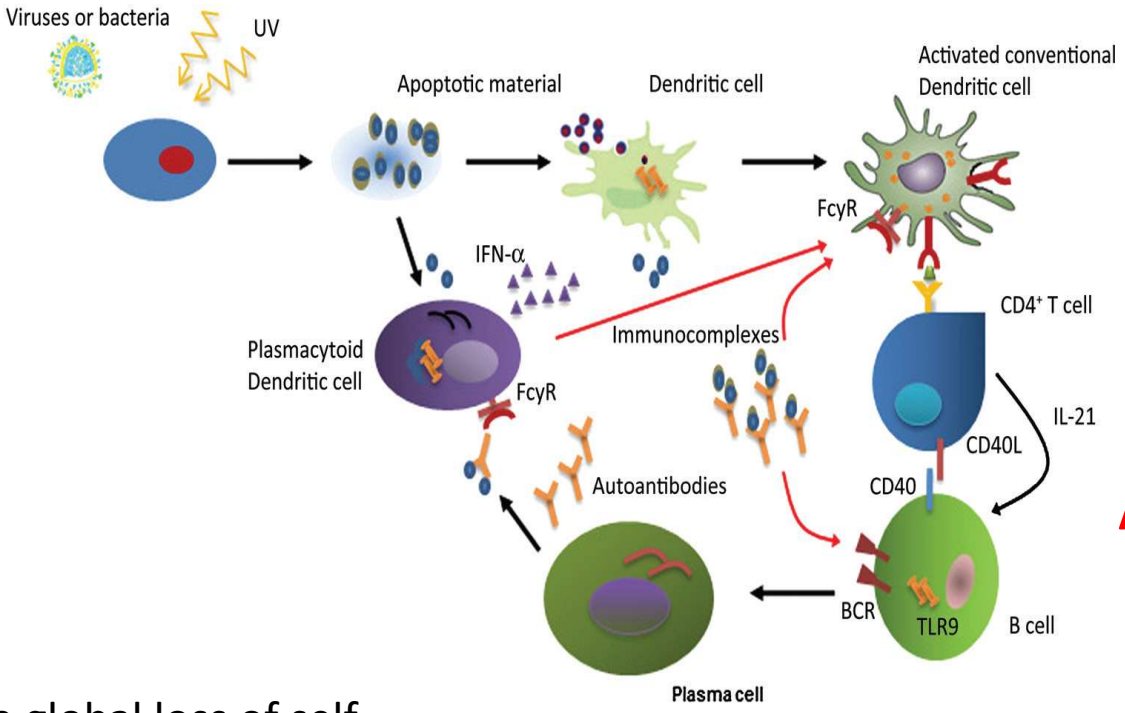
Immunological Mechanisms

- TWO- STAGE DISEASE
  - **Loss of self-tolerance/Auto-Abs generation:** Involves self-antigen presentation by DCs
  - **Immune complex formation:** causes inflammation/disease


Environmental / Epigenetic Influences
Diet
Smoking
Vitamin D
Metals
Medications
Infections (EBV)
Pesticides
Other exposures
Silica
Microbiome
Solvents
Genetic Predisposition
Loss of tolerance to self antigens
Development of autoantibodies
Tissue damage & onset of symptoms
Clinical Disease

Pathogenesis

Innate

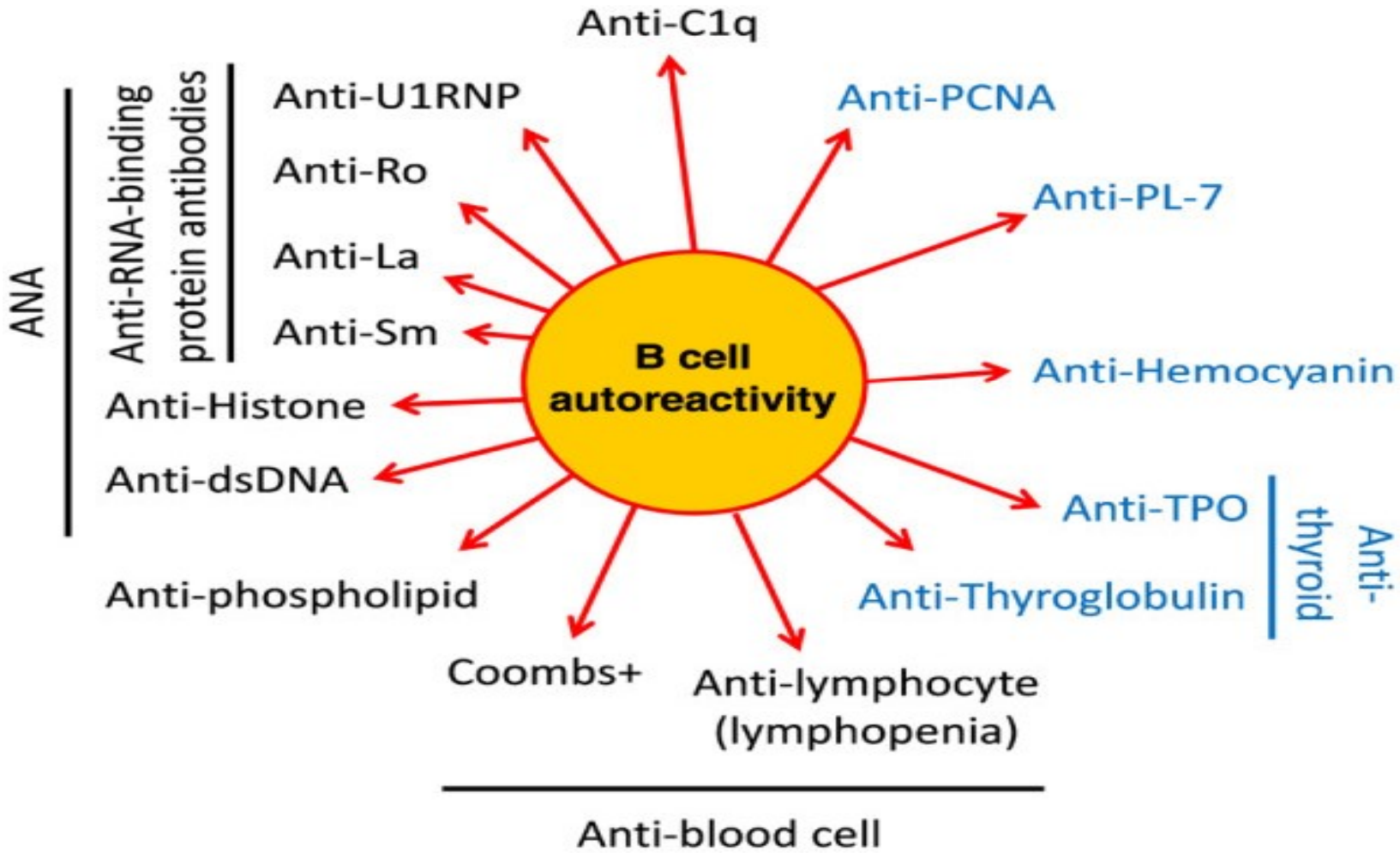


Adaptive

SLE is characterized by a global loss of self-tolerance with activation of autoreactive T and B cells leading to production of pathogenic autoantibodies and tissue injury

Ann Rheum Dis 2010;69:1603–11

Pathogenesis



www.dressage-de-chien.net

Table 3. Common Agents That Cause DIL[a]

Drug	Risk
Acebutolol	Low
Carbamazepine	Low
Chlorpromazine	Low
Hydralazine	High
Isoniazid	Low
Methyldopa	Low
Minocycline	Low
Penicillamine	Low
Procainamide	High
Quinidine	Moderate
Sulfasalazine	Low

[a] Insufficient data at this time to assess the risk for anti-TNF-alpha agents.
DIL: drug-induced lupus; TNF: tumor necrosis factor.
Source: References 1, 2, 7, 8, 11.

Cumulative frequencies of SLE features

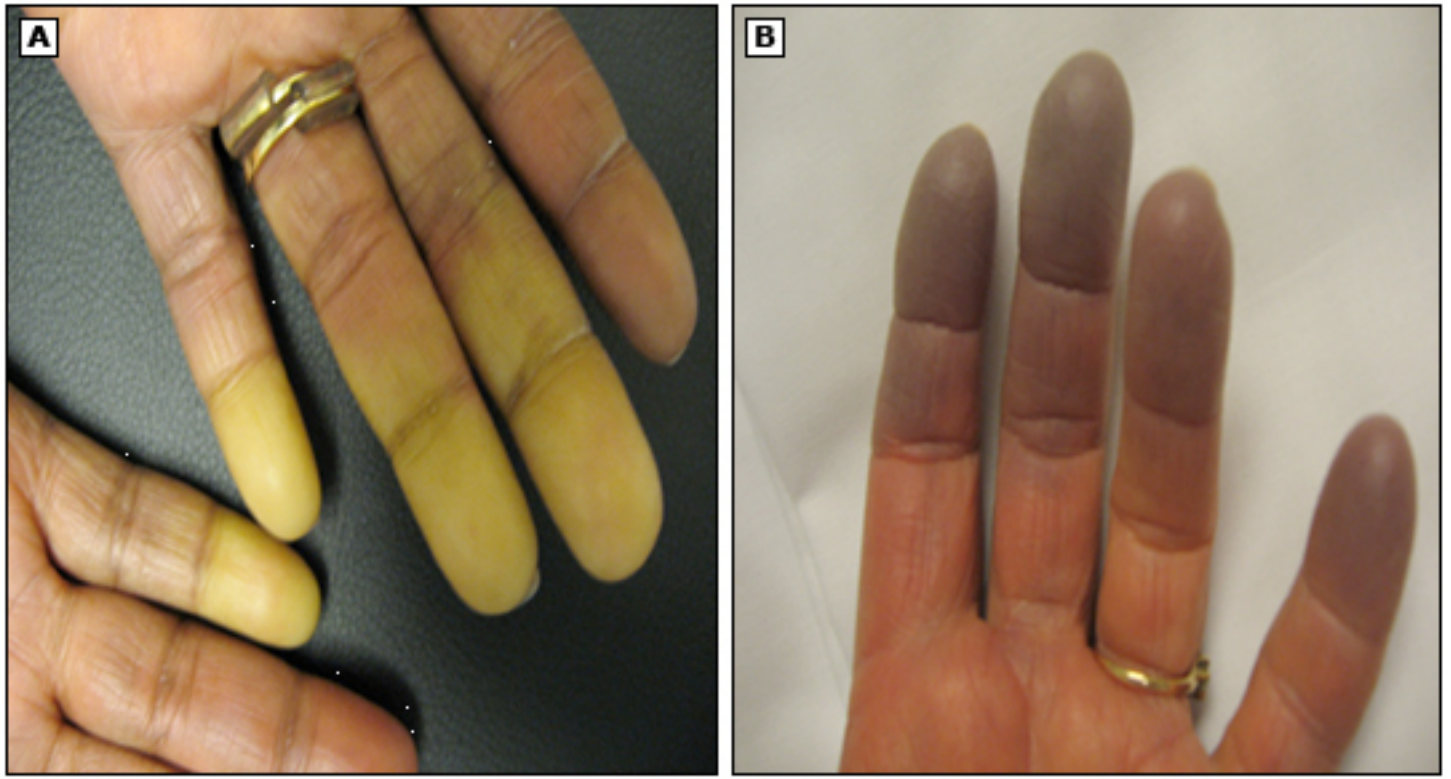
Manifestation	Frequency
Constitutional symptoms	90%-95%
Mucocutaneous involvement	80%-90%
Musculoskeletal involvement	80%-90%
Serositis	50%-70%
Glomerulonephritis	40%-60%
Neuropsychiatric involvement	40%-60%
Autoimmune cytopenia	20%-30%

Frequency of signs and symptoms of systemic lupus erythematosus

Signs and symptoms	Percent at onset	Percent at any time
Fatigue	50	74 to 100
Fever	36	40 to 80+
Weight loss	21	44 to 60+
Arthritis or arthralgia	62 to 67	83 to 95
Skin	73	80 to 91
Butterfly rash	28 to 38	48 to 54
Photosensitivity	29	41 to 60
Mucuous membrane lesion	10 to 21	27 to 52
Alopecia	32	18 to 71
Raynaud's phenomenon	17 to 33	22 to 71
Purpura	10	15 to 34
Urticaria	1	4 to 8
Renal	16 to 38	34 to 73
Nephrosis	5	11 to 18
Gastrointestinal	18	38 to 44
Pulmonary	2 to 12	24 to 98
Pleurisy	17	30 to 45
Effusion		24
Pneumonia		29
Cardiac	15	20 to 46
Pericarditis	8	8 to 48
Murmurs		23
ECG changes		34 to 70
Lymphadenopathy	7 to 16	21 to 50
Splenomegaly	5	9 to 20
Hepatomegaly	2	7 to 25
Central nervous system	12 to 21	25 to 75
Functional		Most
Psychosis	1	5 to 52
Convulsions	0.5	2 to 20

Adapted from: Von Feldt JM, Postgrad Med 1995; 97:79.

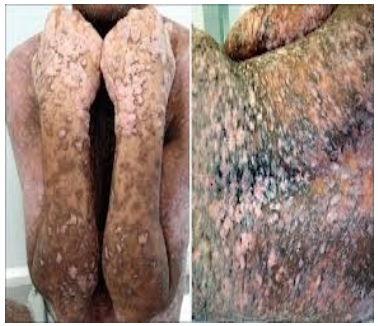
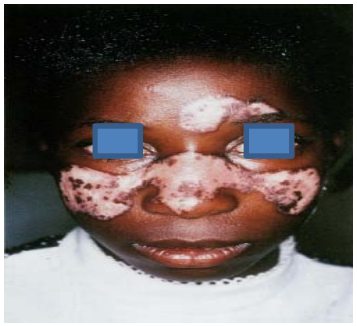
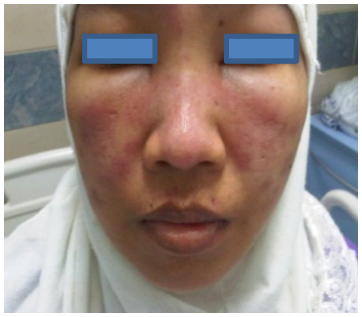
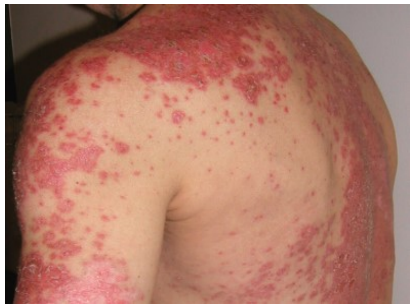
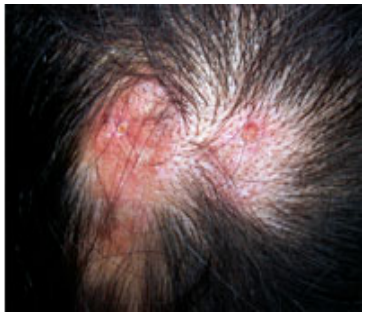
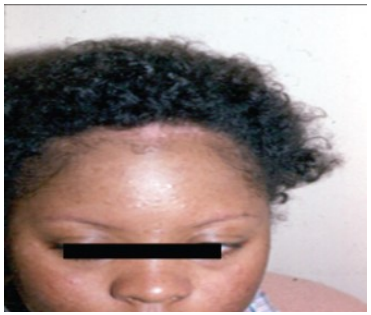
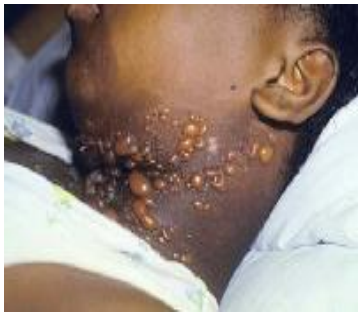
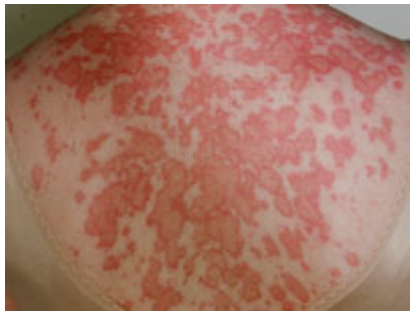
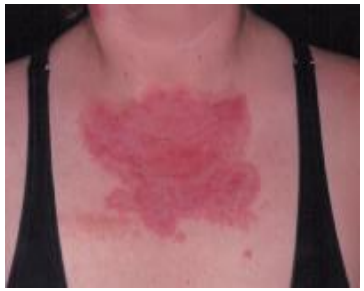
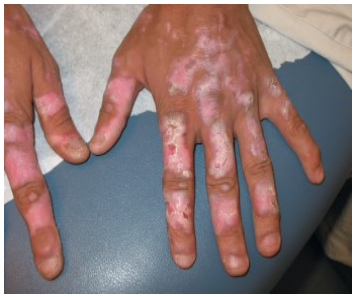
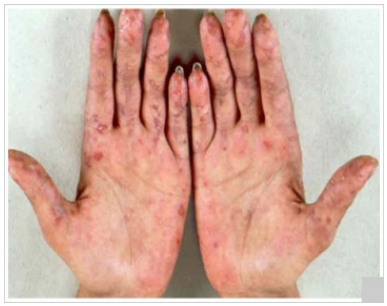
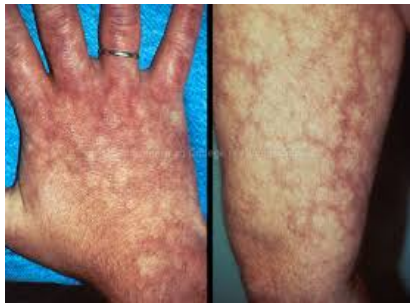
Raynaud phenomenon



Panel A shows sharply demarcated pallor in several fingers resulting from the closure of digital arteries.
Panel B shows digital cyanosis of the fingertips resulting from vasoconstriction in the thermoregulatory vessel in the skin.

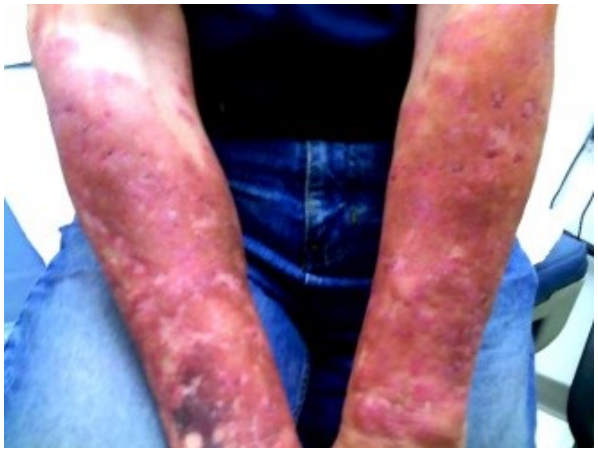
Courtesy of Fredrick M Wigley, MD.

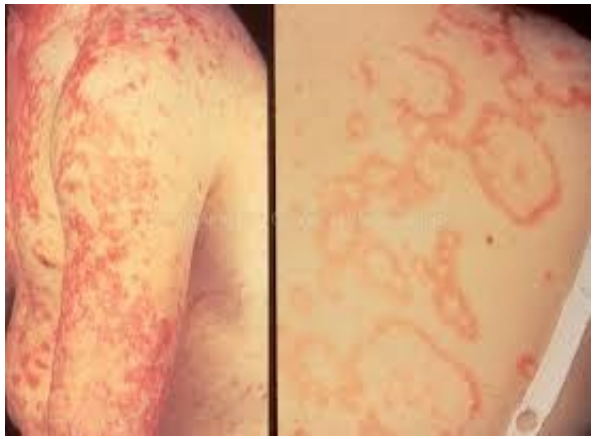
SLE- Cutaneous manifestations

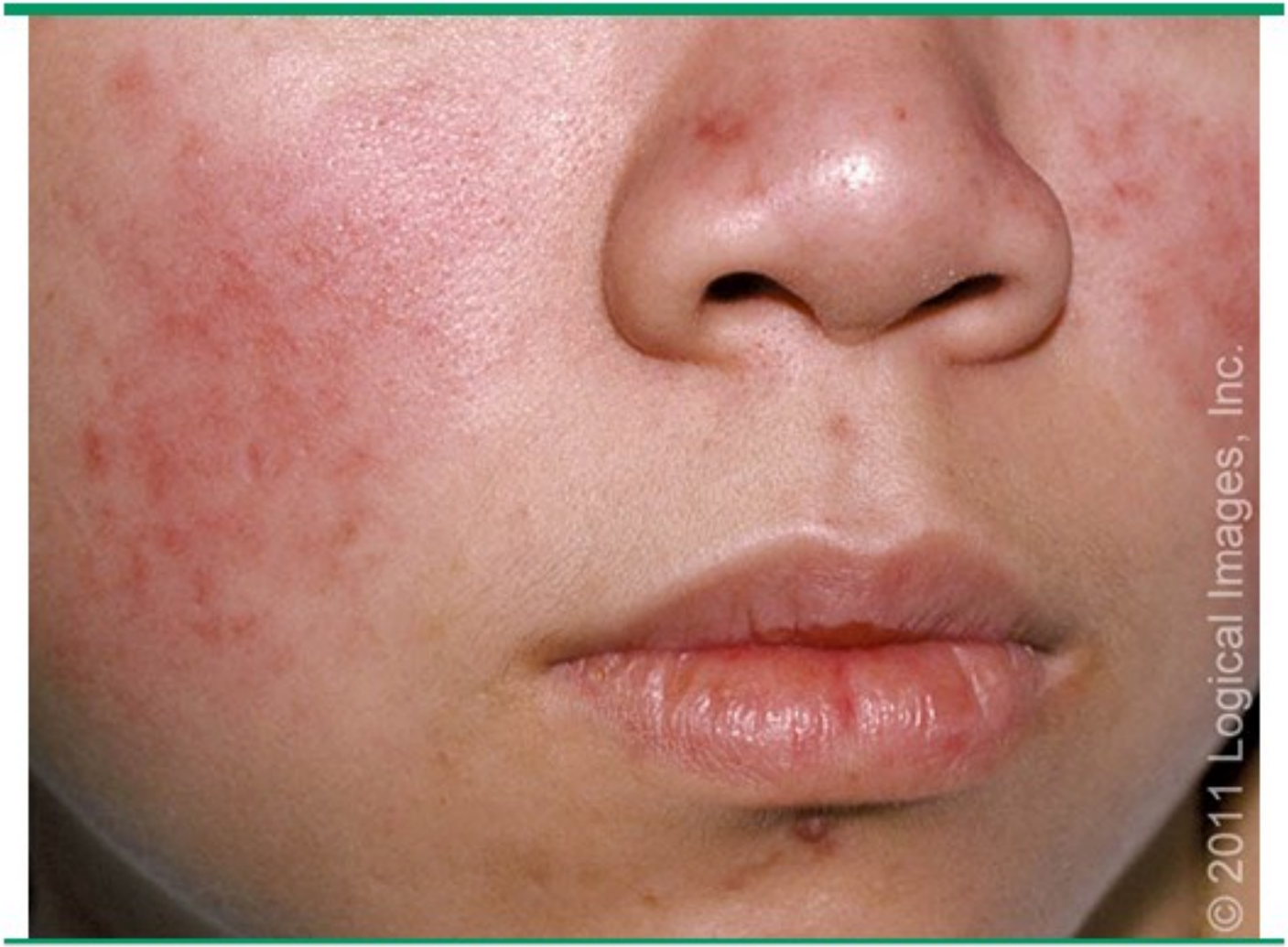
Acute Cutaneous / Subacute Cutaneous Lupus

- Malar rash
- Bullous lupus
- Toxic epidermal necrolysis
- Maculopapular lupus rash
- Photosensitive lupus rash
- Nonindurated psoriasiform
- Annular polycyclic rash



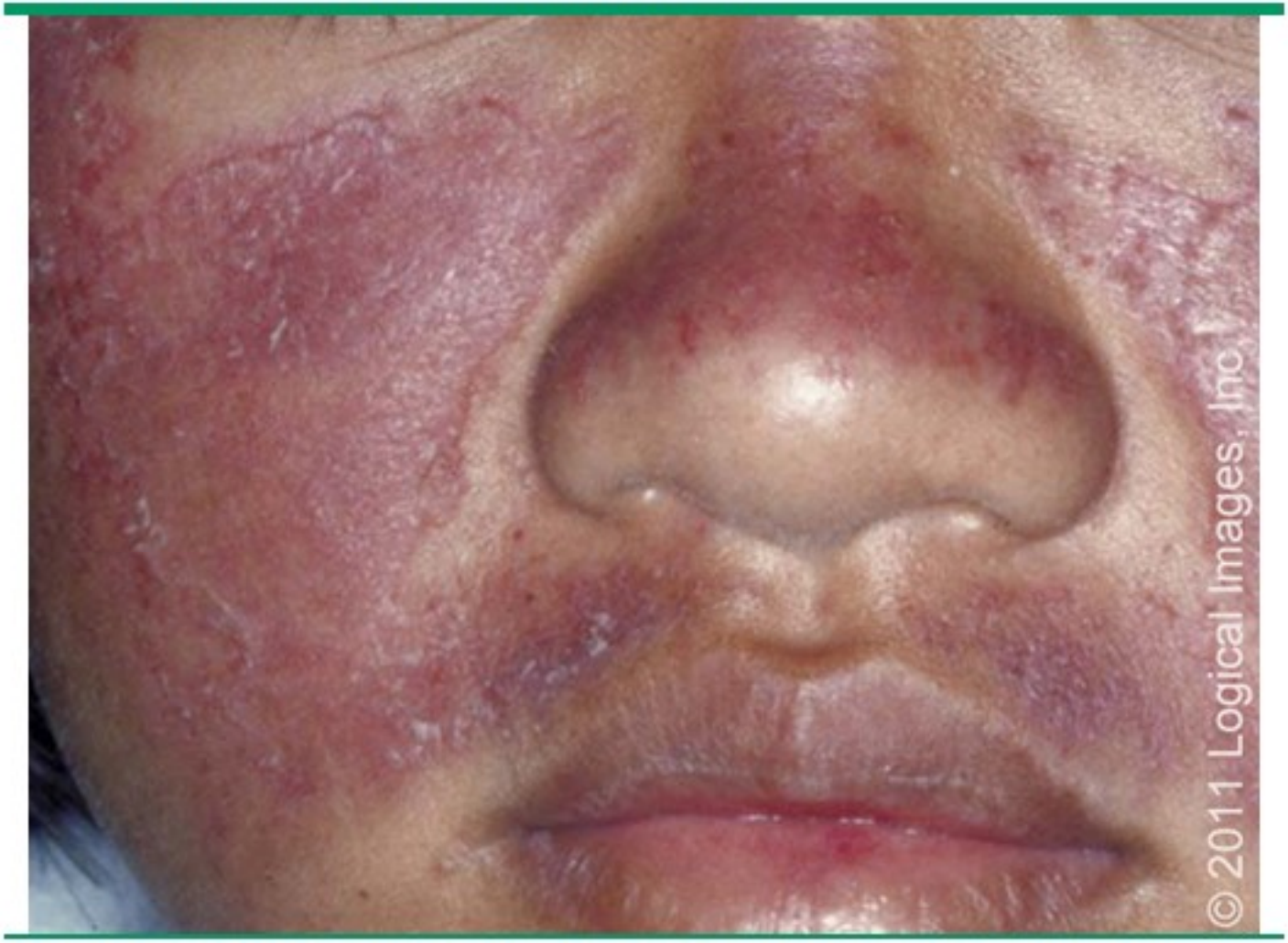


Acute cutaneous lupus erythematosus



Malar erythema and subtle edema are present in this patient with systemic lupus erythematosus.

Acute cutaneous lupus erythematosus

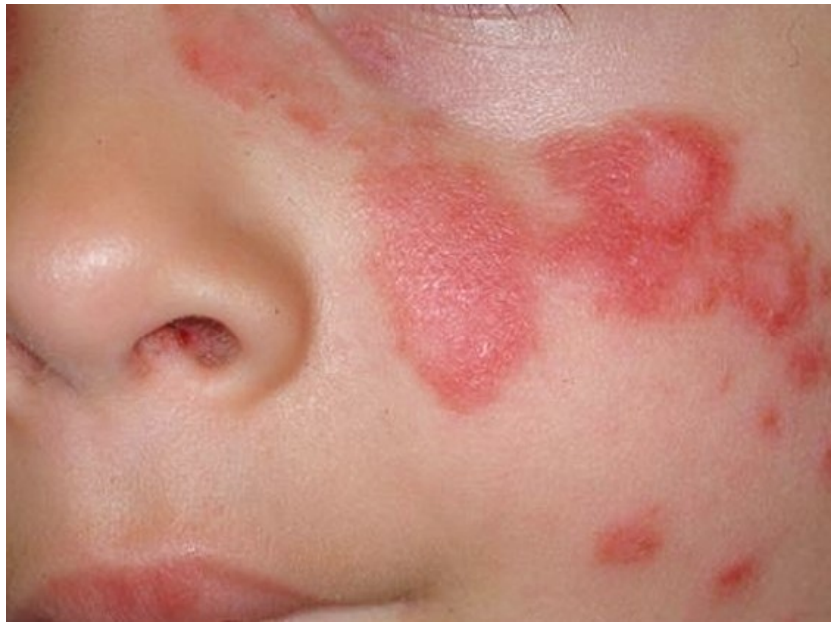


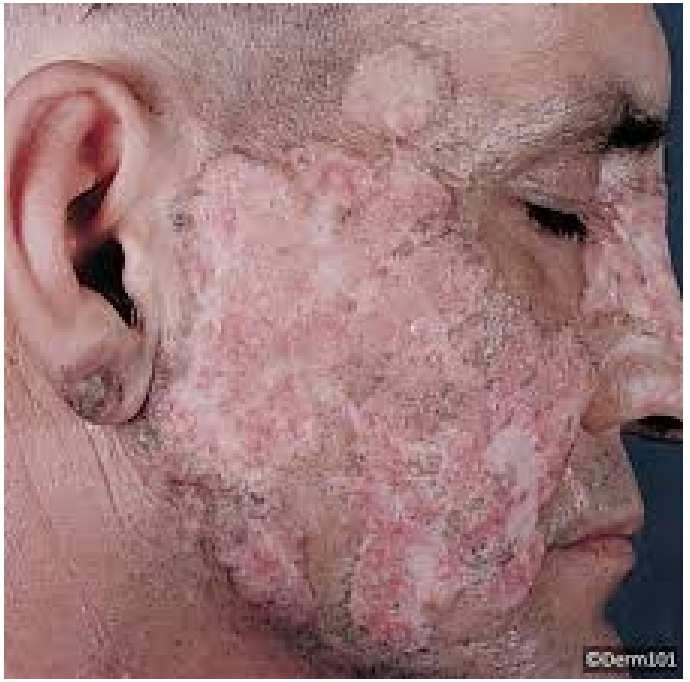
An erythematous, edematous eruption is present on the malar area. Note the sparing of the nasolabial folds.

Chronic Cutaneous Lupus

- Discoid rash, localized & generalized
- Hypertrophic (verrucous) lupus
- Lupus panniculitis (profundus)
- Lupus erythematosus tumidis
- Chilblains lupus
- Mucosal lupus
- Lichen planus overlap

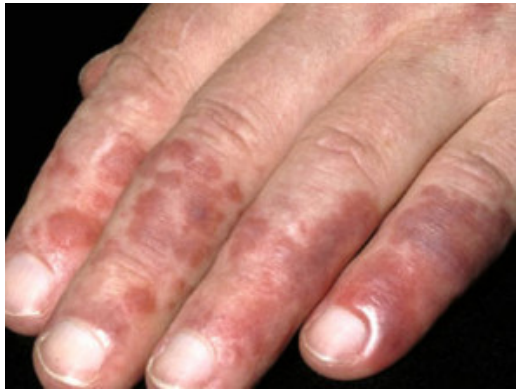
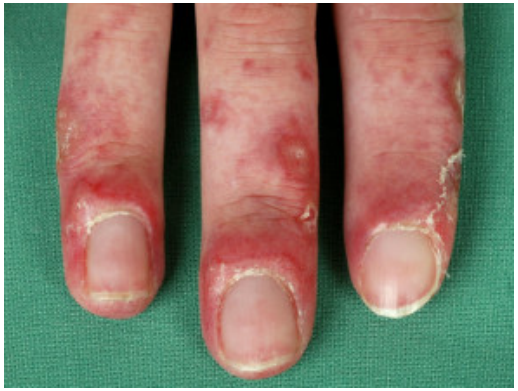
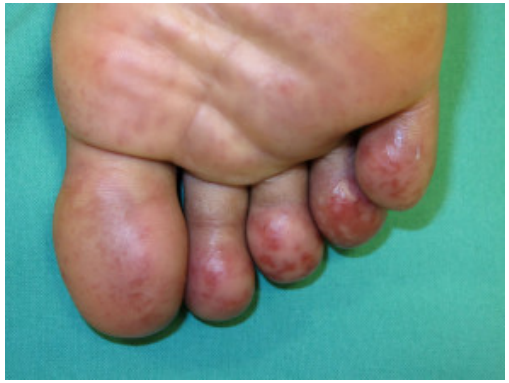
Discoid lupus



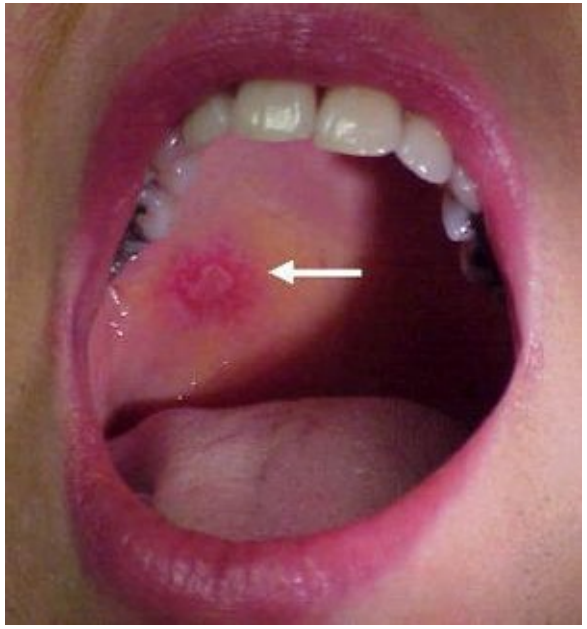


Chilblain LE

- Pruritic and painful Red or dusky purple patches, papules, and plaques that are initiated or exacerbated by exposure to cold and moisture in a cool climate.
- Fingers, toes, heels, and soles.

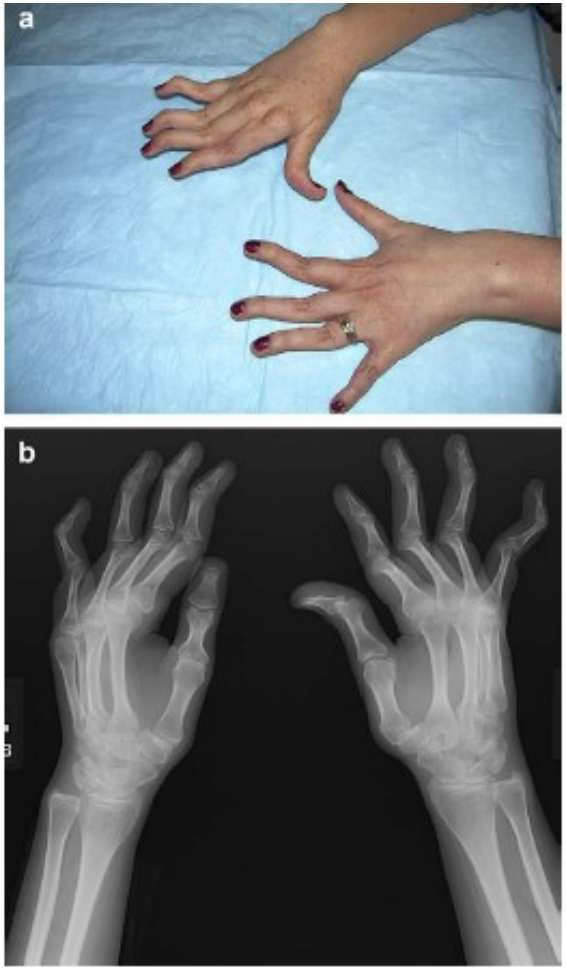
Oral and nasal ulcers



Arthritis

- Symmetric non-deforming polyarthritis
- The most common joints affected are the hand joints including the metacarpal phalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) as well as the knees
- occasionally develop deformities, which could be erosive or nonerosive.
- Jaccoud's arthropathy: a variant of lupus arthritis resulting from ligament laxity and joint subluxation.

Jaccoud’s arthropathy



Renal disease

WHO Classification of Lupus Nephritis

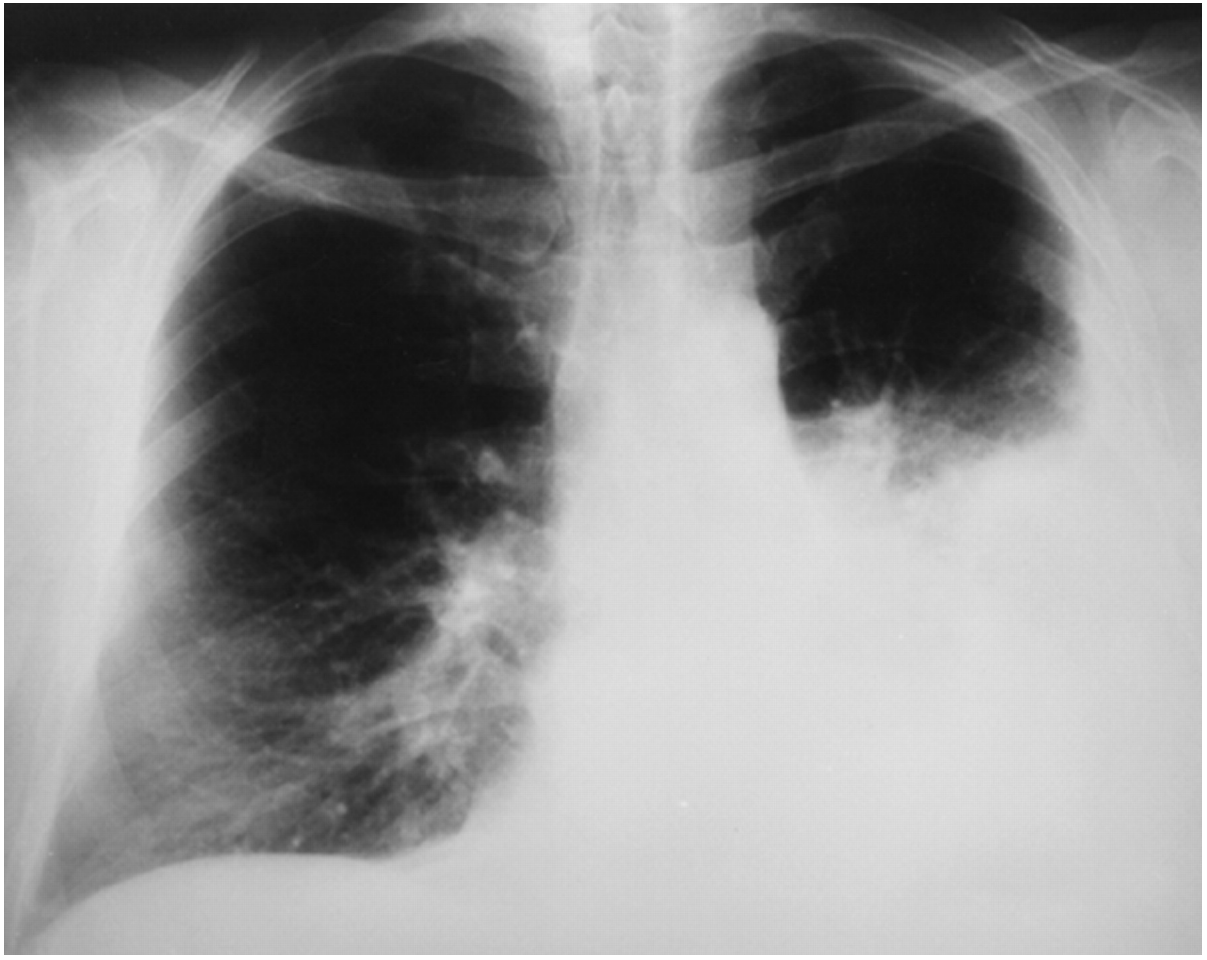
CLASS I	**Minimal Mesangial Glomerulonephritis** - histologically normal on light microscopy but with mesangial deposits on electron microscopy
CLASS II	**Mesangial Proliferative Lupus Nephritis** - typically responds completely to treatment with corticosteroids
CLASS III	**Focal Proliferative Nephritis** - often successfully responds to treatment with high doses of corticosteroids
CLASS IV	**Diffuse Proliferative Nephritis** - mainly treated with corticosteroids and immunosuppressant drugs
CLASS V	**Membranous Nephritis** - characterized by extreme edema and protein loss
CLASS VI	**Glomerulosclerosis**

Pulmonary disease

- The most common thoracic manifestation of SLE is pleuritis
- Acute lupus pneumonitis
- Diaphragmatic dysfunction
- Shrinking lung syndrome
- Cavitating pulmonary nodules
- Pulmonary hypertension
- Pulmonary vasculitis
- Pulmonary embolism (often due to circulating anticardiolipin antibodies)
- Alveolar haemorrhage (reflecting diffuse endothelial injury)
- Chronic interstitial pneumonitis
- Bronchiolitis obliterans (with or without organising pneumonia)

Opportunistic pulmonary infections or drug toxicity from immunosuppressive therapy

Lupus pneumonitis



Approach to SLE diagnosis

- No gold standard test
- Clinical reasoning
- Classification criteria

Diagnostic workup

- Identify disease manifestations
- Perform Lab. Tests
- Exclude other diseases
- Distinguish ***ACTIVITY*** from ***CHRONICITY***
- Prioritize active disease manifestations

Approach to SLE diagnosis

HISTORY:

- Constitutional symptoms such as fever, fatigue, lymphadenopathy, or weight loss
- Photosensitive skin lesions such as a malar rash
- Painless oral or nasal ulcers
- Hair loss that is patchy or frontal/peripheral
- Raynaud phenomenon
- Joint pain or swelling which can be migratory or symmetrical
- Dyspnea or pleuritic chest pain suggestive of serositis
- Chest pain suggestive of pericarditis
- Lower extremity edema
- Neurologic symptoms such as seizures or psychosis
- Recurrent miscarriages

Ask about exposure to medications associated with drug-induced lupus

Approach to SLE diagnosis

PHYSICAL EXAMINATION

A complete physical examination is indicated, since any organ system can be involved in SLE.

Pertinent physical examination findings include the following:

- Skin lesions consistent with a malar rash or discoid lesions
- Scarring or nonscarring patchy alopecia
- Oral or nasopharyngeal ulcers
- Polyarticular arthritis which is often symmetric
- Decreased or abnormal breath sounds may indicate a pleural effusion, pneumonitis, or interstitial lung disease
- Lower extremity edema and hypertension may be due to renal involvement

Approach to SLE diagnosis

LABORATORY TESTING:

- Complete blood count and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia
- Elevated serum creatinine may be suggestive of renal dysfunction
- Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts
- ANA
- Antiphospholipid antibodies (lupus anticoagulant [LA], IgG and IgM anticardiolipin [aCL] antibodies; and IgG and IgM anti-beta2-glycoprotein [GP]
- C3 and C4 or CH50 complement levels
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels
- Urine protein-to-creatinine ratio

LABORATORY TESTING:

The ANA test is positive in all patients with SLE at some time in the course of their disease

If the ANA is positive:test for other specific antibodies such as dsDNA, anti-Sm, Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP).

If the initial ANA test is negative, but the clinical suspicion of SLE is high, then additional antibody testing may still be appropriate. This is partly related to the differences in the sensitivity and specificity among the methods used to detect ANA.

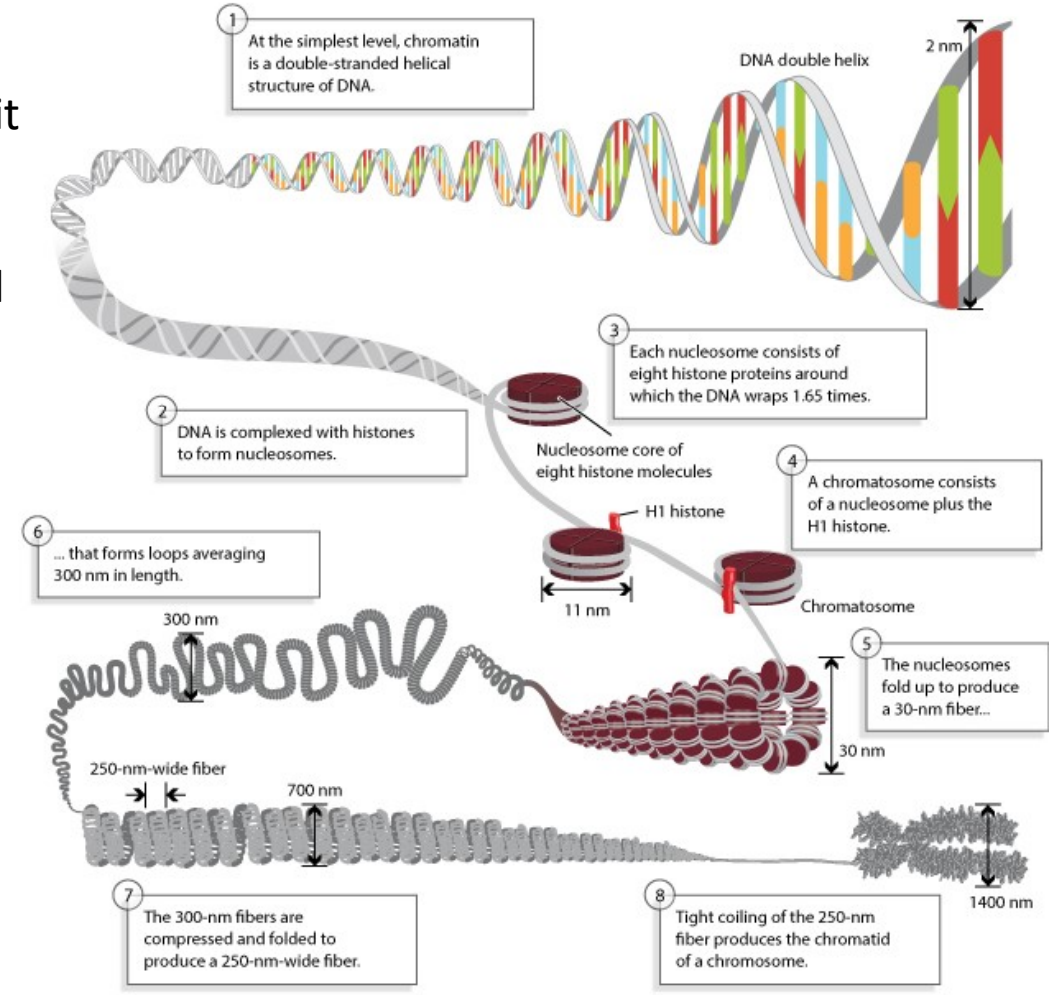
Antinuclear Antibodies :ANA

- Autoantibodies that bind to contents of the cell nucleus
- Most ANA are directed against nucleic acids or proteins associated with nucleic acids
- In systemic lupus erythematosus (SLE), the most predominant antigen is the nucleosome.

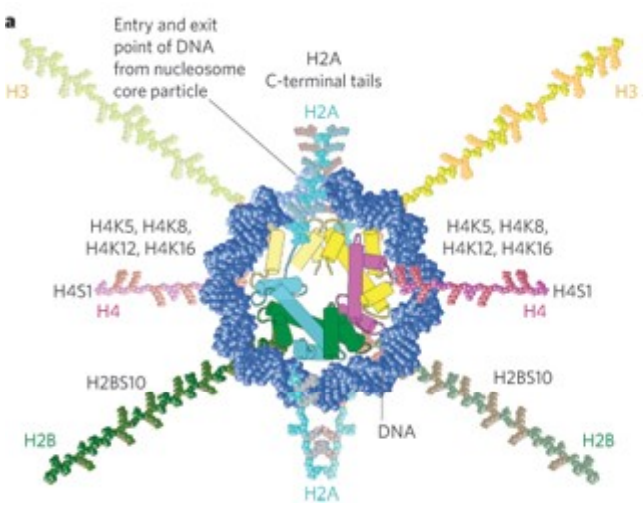
The Nucleosome

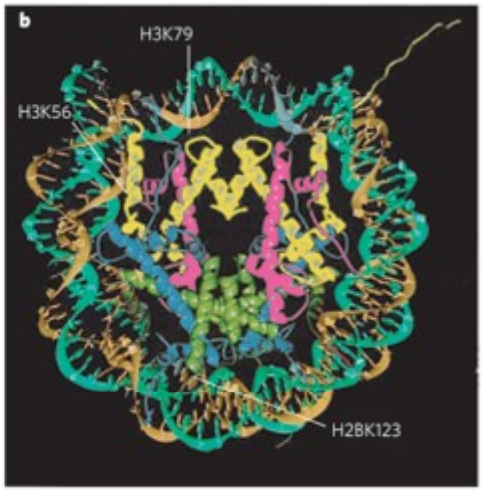
Nucleosome is a basic unit of DNA packaging.

A segment of DNA wound in sequence around eight histone protein cores.



Nucleosome Core Particle



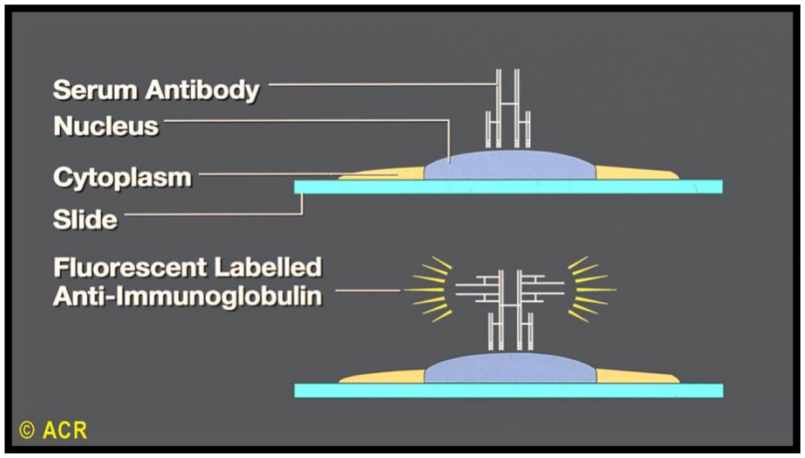


- Each nucleosome core particle consists of double-stranded DNA wrapped around two molecules of each of the four core histone proteins: H2A, H2B, H3 and H4

Review Article Chromatin dynamics and the preservation of genetic information
Jessica A. Downs[1], Michel C. Nussenzweig[2] & André Nussenzweig[3] *Nature* **447**, 951-958 (21 June 2007) | doi:10.1038/nature05980; Published online 20 June 2007

ANA detection Methods

Indirect immunofluorescence (IIF)

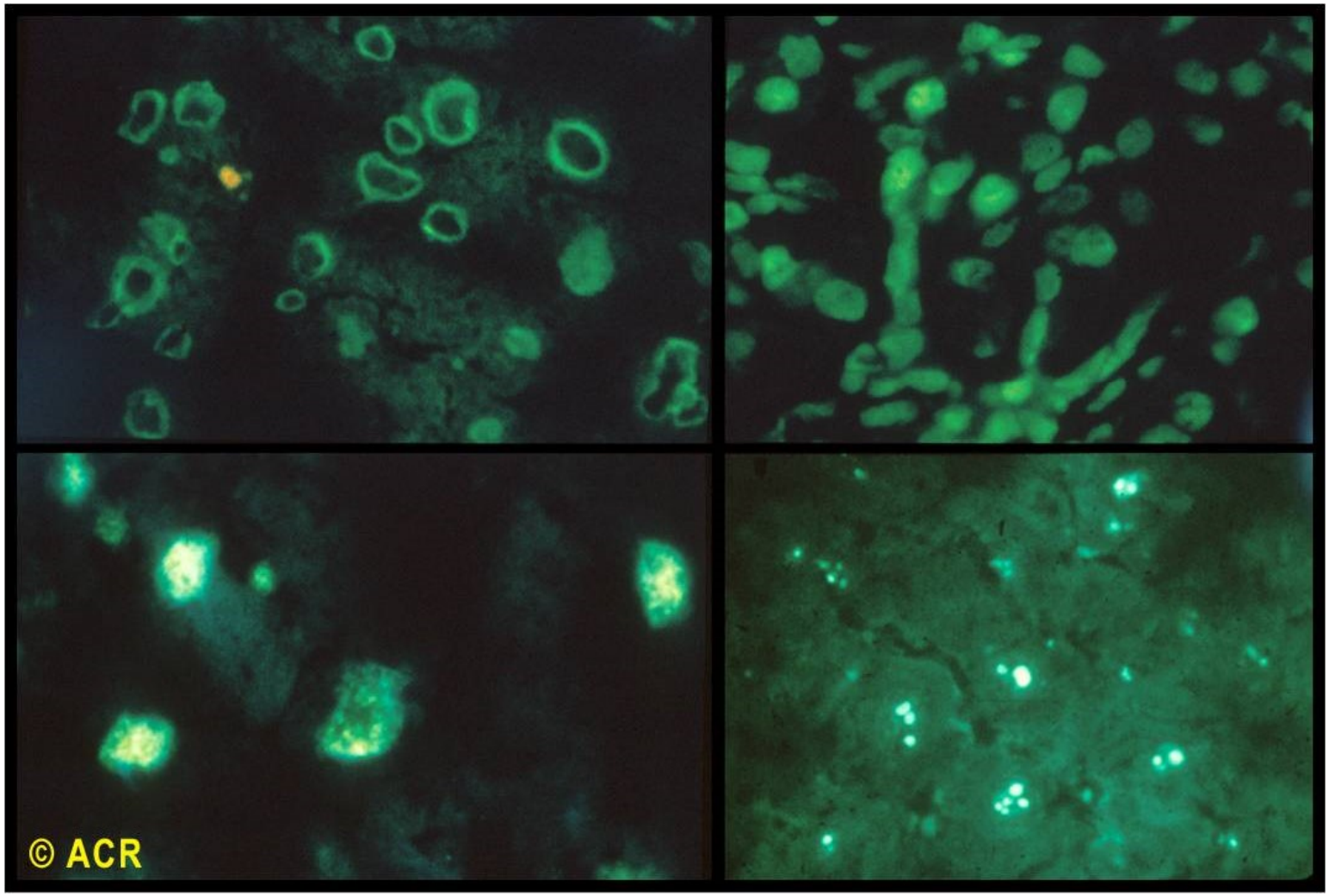


- The most widely used assay for the detection of ANA
- Human epidermoid carcinoma cell line (HEp-2) cell substrate
- HEp-2 cells are grown >> fixed to glass slides, add diluted patient serum >> incubation>>> slides washed to remove nonadherent immunoglobulins >> cells incubated with a fluorescein-conjugated antibody directed against human immunoglobulin.
- The fluorescein-conjugated secondary antibodies bind to human antibodies, which have reacted with antigens present in the HEp-2 cell substrate.
- Slides are examined using an ultraviolet microscope.

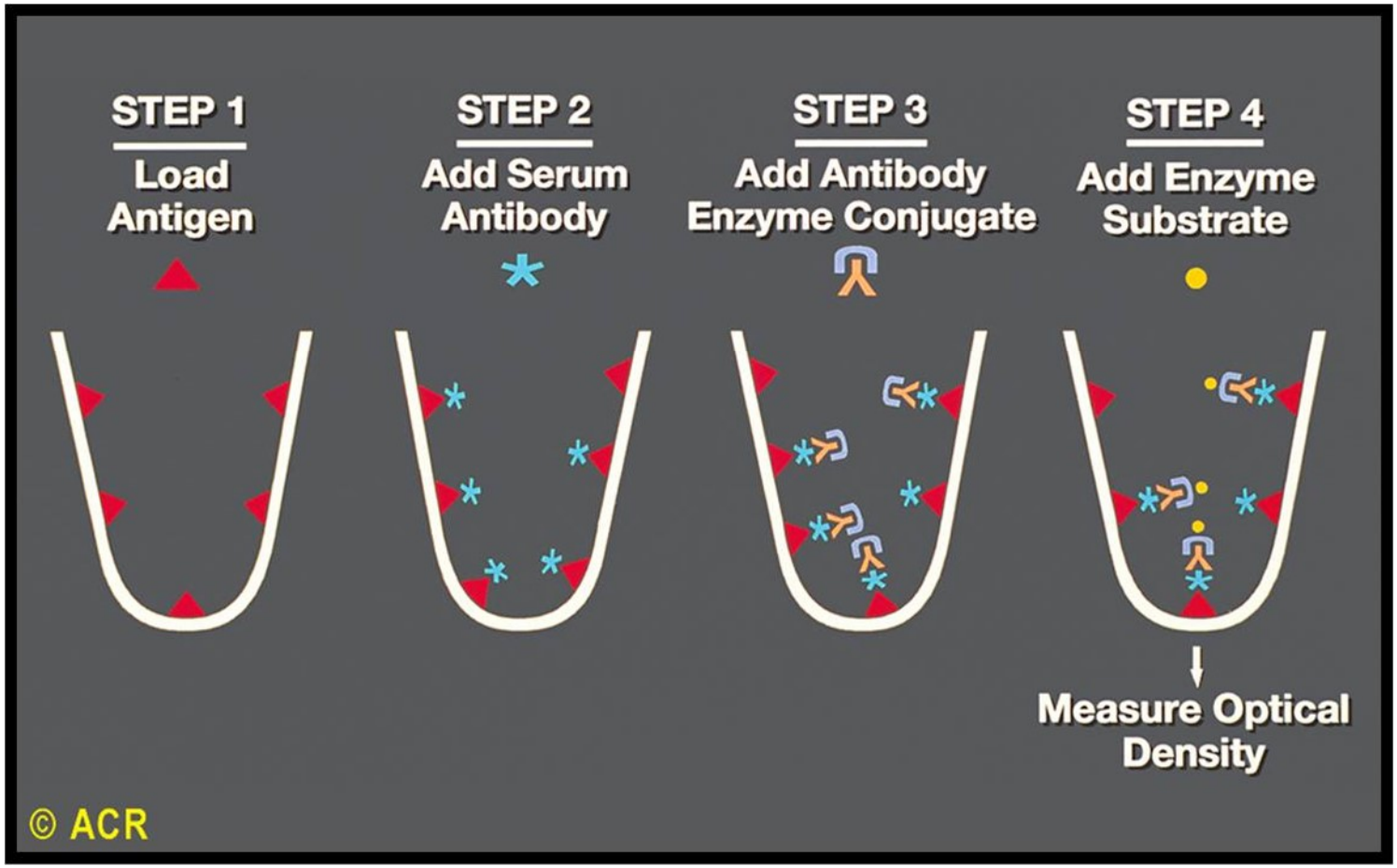
ANA detection methods: Indirect immunofluorescence

- If fluorescence is detected at one or more screening dilutions (often 1:40 and 1:160), the serum is serially diluted and retested.
- An endpoint is reached when fewer than half of the cells on the slide show detectable fluorescence.
- The ANA titer is reported as the dilution prior to this endpoint.
- American College of Rheumatology : IIF using HEp-2 cells should be the “gold standard” for ANA screening
- Disadvantages: labor intensive slide processing, manual reading, the need for experienced, trained technologists and the use of dark room

ANA staining pattern in IF



ANA detection methods:
ELISA



Subtypes of ANAs based on the target of the antibody

- **Autoantibodies to DNA and histones**

❑ **1- Single and double-stranded DNA (dsDNA)**

- Anti-DsDNA antibodies : Nearly 100% specific for SLE
- Correlates well with renal disease activity of lupus
- Probably pathogenic
- Moderate sensitivity (70%)
- Can be caused by drugs: infliximab, minocycline, d-PEN
- One of ACR Classification criteria for SLE
- May be ordered for the cases of positive ANA and clinical suspicion for SLE

❑ **2- Anti-histone antibodies :**

Drug-induced SLE

Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited
Yashwant Kumar[1*], Alka Bhatia[2] and Ranjana Walker Minz[3]

- **Autoantibodies to extractable nuclear antigens (ENA)**

- **ENA:** originally were extracted from the nuclei with saline.

❑ **1- Smith antigen (Sm)** : specific for SLE

- Speckled ANA
- ELISA
- One of ACR Classification Criteria for SLE
- Indication: Clinical suspicion for SLE

Autoantibodies to extractable nuclear antigens (ENA)

❑ 2- Ribonucleoproteins (RNP):

- Speckled ANA
- ELISA
- Diagnostic of Mixed Connective Tissue Disease
- Can be seen in SLE but usually with Sm or ds-DNA
- Indication: Clinical suspicion for MCTD or SLE

Autoantibodies to extractable nuclear antigens (ENA)

❑ 3- SSA/Ro and SSB/La:

- ➢ Sjogren's.
- ➢ ANA-negative lupus (very photosensitive lupus) and Subacute cutaneous lupus (SSA)
- ➢ May protect against renal disease
- ➢ Isolated La/SS-B in autoimmune hepatitis and PBC
- • Indications: Clinical suspicion for SLE or Sjogren's

Autoantibodies to extractable nuclear antigens (ENA)

- **4- Anti Scl-70:** (Anti-topoisomerase I)
  - Nucleolar ANA pattern
  - Very specific for diffuse Systemic sclerosis but not sensitive
  - Associated with interstitial lung disease

Autoantibodies to extractable nuclear antigens (ENA)

- **5- anti Jo-1** (Anti-synthetase)

- Highly specific for Polymyositis/Dermatomyositis
- Antisynthetase syndrome
- Interstitial lung disease, mechanics hands, arthritis, Raynaud's

Pathogenic role of ANA

- Most ANA seem not involved in pathogenesis

- ANA is caused by disease rather than to be the cause of disease
- Pathogenic role of DS DNA: lupus nephritis
- Anti-Ro/SS-A and maybe anti-La/SS-B : involved in the pathogenesis of congenital heart block
- Anti-Ro/SS-A and anti-La/SS-B in adults seem to be caused by ‘disease’ only

  >> found in mothers of CHB children

Interpreting ANA results

- Look for the staining pattern (although the association is weak) and titer if positive ANA by IIF

- If ANA is negative by IIF: no further testing unless the clinical suspicion of systemic lupus erythematosus (SLE) or other ANA-associated autoimmune disease is high

- ANA may also be detected in healthy subjects who have first-degree relatives with autoimmune diseases

Interpreting ANA results

- ANA may also develop in patients who are taking certain medications with or without full blown drug-induced autoimmune disease.

- ANA may develop years before the symptoms of autoimmune disease

✓ 5% of healthy controls positive at 1:160 dilution

✓ 10-15% of healthy controls positive at 1:80 dilution

✓ 30% of healthy controls positive at 1:40 dilution

- 1:80 AND 1:40 are normal large majority of the time

ANA-negative lupus

- Influenced by the testing methods used to detect ANA
- On rare occasions, the presence of anti-Ro antibodies may suggest a systemic autoimmune disease, despite the presence of a negative ANA indirect immunofluorescence.
- We should understand the technique used to detect the ANA since this can influence the result.
- Disease duration and treatment exposure : ?? some SLE patients who have longstanding disease and/or have undergone treatment may lose ANA reactivity and become serologically negative over time.

Diseases associated with a positive ANA

	Percent with positive ANA
Systemic autoimmune diseases	
SLE	
Active	98 to 100 percent
Remission	90 percent
Scleroderma	95 percent
Rheumatoid arthritis	45 percent
Sjögren's syndrome	60 percent
Mixed connective tissue disease	100 percent
Drug-induced LE	80 to 95 percent
Raynaud's phenomenon	40 percent
Polymyositis/dermatomyositis	35 percent
Juvenile idiopathic arthritis	15 to 40 percent
Organ-specific autoimmune diseases	
Hashimotos thyroiditis	50 percent
Graves' disease	50 percent
Autoimmune hepatitis	70 percent
Primary biliary cirrhosis	50 to 70 percent
Infectious diseases*	
Viral:	
EBV	
HIV	
HCV	
Parvovirus 19	
Bacterial:	
SBE	
Syphilis	
Malignancies*	
Lymphoproliferative diseases	
Paraneoplastic syndromes	
Miscellaneous diseases*	
Inflammatory bowel disease	
Interstitial pulmonary fibrosis	

ANA: antinuclear antibodies; SLE: systemic lupus erythematosus; EBV: Epstein-Barr virus; HCV: hepatitis C virus; SBE: subacute bacterial endocarditis.

* Although positive tests of ANA are reported in these diseases more often than in healthy controls, precise estimates vary.

Courtesy of Donald B Bloch, MD.

Features of spontaneous and drug-induced lupus

Clinical feature	Idiopathic SLE	Drug-induced lupus
Gender predisposition (F:M)	9:1	1:1
Acetylation type	Slow = Fast	Slow (described for hydralazine and procainamide)
Symptom onset	Gradual	Abrupt
Usual age	20 to 40	Drug-dependent, tends to be older population than idiopathic (>50)*
Race	All	Less likely to occur in black patients
Fever/malaise	40 to 85 percent	40 to 50 percent
Arthralgias/arthritis	75 to 95 percent	80 to 95 percent
Rash (all)	50 to 70 percent	10 to 30 percent
Rash (discoid)	20 percent	Rare¶
Rash (malar/acute cutaneous)	42 percent	2 percent
Raynaud's	35 to 50 percent	<25 percent
Pleuritis/pleural effusion	16 to 60 percent	10 to 50 percent (procainamide)
Pulmonary infiltrates	0 to 10 percent	5 to 40 percent (procainamide)
Pericarditis	6 to 45 percent	2 to 18 percent
Hepatomegaly/splenomegaly	10 to 45 percent	5 to 25 percent
Renal involvement	30 to 50 percent	0 to 5 percent
CNS/neurologic involvement	25 to 70 percent	0 to 2 percent
Hematologic	Common	Unusual
Laboratory feature	**Idiopathic SLE**	**Drug-induced lupus**
ANA	95 to 98 percent	95 to 100 percent
Anti-dsDNA	50 to 80 percent	<5 percent (rare)
Anti-Smith	20 to 30 percent	<5 percent (rare)
Anti-RNP	40 to 50 percent	20 percent
Anti-Ro/SS-A	30 to 40 percent	Uncertain§
Anti-histone	60 to 80 percent	90 to 95 percentΔ
Low complement levels	40 to 65 percent	Rare
Anemia	30 to 90 percent	0 to 46 percent
Leukopenia	35 to 66 percent	2 to 33 percent
Positive Coombs' test	18 to 65 percent	0 to 33 percent◇

CNS: central nervous system; ANA: anti-nuclear antibody; LE: lupus erythematosus; RNP: ribonucleoprotein; dsDNA: double-stranded deoxyribonucleic acid.

* Minocycline-induced disease tends to occur in young females, consistent with greater use of the medication than other groups.

¶ Case reports of drug-induced discoid lupus with anti-TNF drug exposure.

§ Insufficient data are available to provide an accurate estimate for (systemic) drug-induced lupus. The antibodies are present in 70 to 90 percent of patients with drug-induced subacute cutaneous lupus.

Δ Overall presence of anti-histone antibodies in drug-induced lupus; prevalence varies markedly between implicated drugs (may be less with minocycline or tumor necrosis factor inhibitors, and data are lacking for many agents). (Merola JF. Lupus-like syndromes related to drugs. In: Lupus Erythematosus: Clinical Evaluation and Treatment, Schur PH, Massarotti E. (Eds), Springer, New York, pp. 211-221).

◇ Most common with methyldopa exposure.

LABORATORY TESTING:
Selected patients

- Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies

In patients with predominant arthralgias or arthritis to exclude a diagnosis of rheumatoid arthritis (RA).

- Serological studies for infection: Human parvovirus B19. hepatitis B virus (HBV) and hepatitis C virus (HCV) in patients with multisystemic clinical findings. Testing for Epstein-Barr virus (EBV) infection

- Creatine kinase (CK) –may reflect myositis, which is uncommon in patients with SLE.

Additional workup

- Plain radiographs : rare to see erosions
- Renal ultrasonography: kidney size, rule out obstruction
- Chest radiography (eg, for suspected pleural effusion, interstitial lung disease, cardiomegaly).
- Echocardiography (eg, for suspected pericardial involvement)

- Computed tomography (CT) (eg, for abdominal pain, suspected pancreatitis, interstitial lung disease).
- Magnetic resonance imaging (MRI) (eg, for focal neurologic deficits or cognitive dysfunction).

Additional workup

- **Biopsy** — Biopsy of an involved organ

- Electrocardiography in the assessment of chest pain that may be due to pericarditis or to myocardial ischemia

- Tests to assess for pulmonary embolism in a patient with pleuritic chest pain and dyspnea

- Diffusing capacity for carbon monoxide (DLCO) to assess for suspected pulmonary hemorrhage and to estimate the severity of interstitial lung disease

Undifferentiated connective tissue disease

Patients with signs and symptoms suggestive of a systemic autoimmune disease but do not meet the ACR criteria for SLE or another defined connective tissues disease.

- Outcome of patients who have UCTD at presentation :

➢ Up to one-third of patients have all symptoms and signs disappear over a 10-year follow-up period.

➢ Anywhere from 40 to 60 percent of patients continue to exhibit their initial clinical features

➢ 5 to 30 percent evolve and meet classification criteria for a definite disease, such as SLE, rheumatoid arthritis (RA), scleroderma, or an inflammatory myopathy (myositis)

Patients with UCTD should be followed carefully, encouraged to report new symptoms, and have periodic laboratory testing to assess for the emergence of new clinical features or laboratory findings.

Classification criteria for SLE

Year	American College of Rheumatology (ACR) classification
1971	Criteria for SLE classification developed
1982	Revised classification
1997	Revised again
2012	SLICC SLE Criteria
2019	2019 European League Against Rheumatism/ American College of Rheumatology

1997 ACR Revised classification criteria

	Clinical Criteria
1	Malar Rash
2	Discoid Rash
3	Photosensitivity
4	Oral ulcers
5	Arthritis
6	Serositis
7	Renal Disorder
8	Neurologic Disorder
9	Hematologic disorder
10	Immunologic disorder
11	Antinuclear Antibody

Immunologic disorder
a) Anti-DNA or
b) Anti- Sm or
c) Positive finding of antiphospholipid antibodies based on:
1.Abnormal IgG/ IgM anticardiolipin antibodies
2. Positive Lupus anticoagulant
3. False positive seologic test for syphilis for 6 months

>=4criteria should be present , serially or simultaneously

2012-SLICC classification criteria

At least 1 clinical + at least 1 immunologic

Criteria (for a total of 4)

OR

Lupus Nephritis by biopsy

with ANA or anti-dsDNA antibodies

* Systemic Lupus International Collaborating Clinics

2012-SLICC classification criteria

	Clinical Criteria
1	Acute Cutaneous Lupus
2	Chronic Cutaneous Lupus
3	Oral or nasal ulcers
4	Non-scarring alopecia
5	Arthritis
6	Serositis
7	Renal Disorder
8	Neurologic Disorder
9	Hemolytic anemia
10	Leukopenia/ Lymphopenia
11	Thrombocytopenia

Lupus specific

2012-SLICC classification criteria

	Immunologic Criteria
1	ANA
2	Anti-DNA
3	Anti- Sm
4	Antiphospholipid antibodies • Lupus anticoagulant; False+ rapid plasma reagin • Anticardiolipin , IgA, IgG or IgM • Anti-B2-glycoprotein I ,IgA, IgG or IgM
5	Low complements (C3,C4 or CH 50)
6	Direct Coombs test (in absence of hemolytic anemia)

Table 1 Definitions of SLE classification criteria

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titre of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leucopenia	White blood cell count <4.0×10∧9/l
Thrombocytopenia	Platelet count <100×10∧9/l
Autoimmune haemolysis	Evidence of haemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH) AND positive Coomb's (direct antiglobulin) test.
Delirium	Characterised by (1) change in consciousness or level of arousal with reduced ability to focus, (2) symptom development over hours to <2 days, (3) symptom fluctuation throughout the day, (4) either (4a) acute/subacute change in cognition (eg, memory deficit or disorientation), or (4b) change in behaviour, mood, or affect (eg, restlessness, reversal of sleep/wake cycle)
Psychosis	Characterised by (1) delusions and/or hallucinations without insight and (2) absence of delirium
Seizure	Primary generalised seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician*
Oral ulcers	Oral ulcers observed by a clinician*
Subacute cutaneous or discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician*: Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed Discoid lupus erythematosus observed by a clinician*: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/haematological(scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present. Subacute cutaneous lupus: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Discoid lupus: interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition and basement membrane thickening may be noted

Acute cutaneous lupus	Malar rash or generalised maculopapular rash observed by a clinician If skin biopsy is performed, typical changes must be present: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, X-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) electrocardiogram (EKG) with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, X-ray, CT scan, MRI)
Joint involvement	EITHER (1) synovitis involving two or more joints characterised by swelling or effusion OR (2) tenderness in two or more joints and at least 30 min of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24 hours urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immune-fluorescence or electron microscopy, but not by light microscopy Class V: membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphological sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class III or IV lupus nephritis on renal biopsy according to International Society of Nephrology/ Renal Pathology Society (ISN/RPS) 2003	Class III: focal lupus nephritis: active or inactive focal, segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: diffuse lupus nephritis: active or inactive diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titre (>40 A phospholipids (APL), GPL or MPL units, or >the 99th percentile) or positive anti-β2GP1 antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Smith (Sm) antibodies.	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

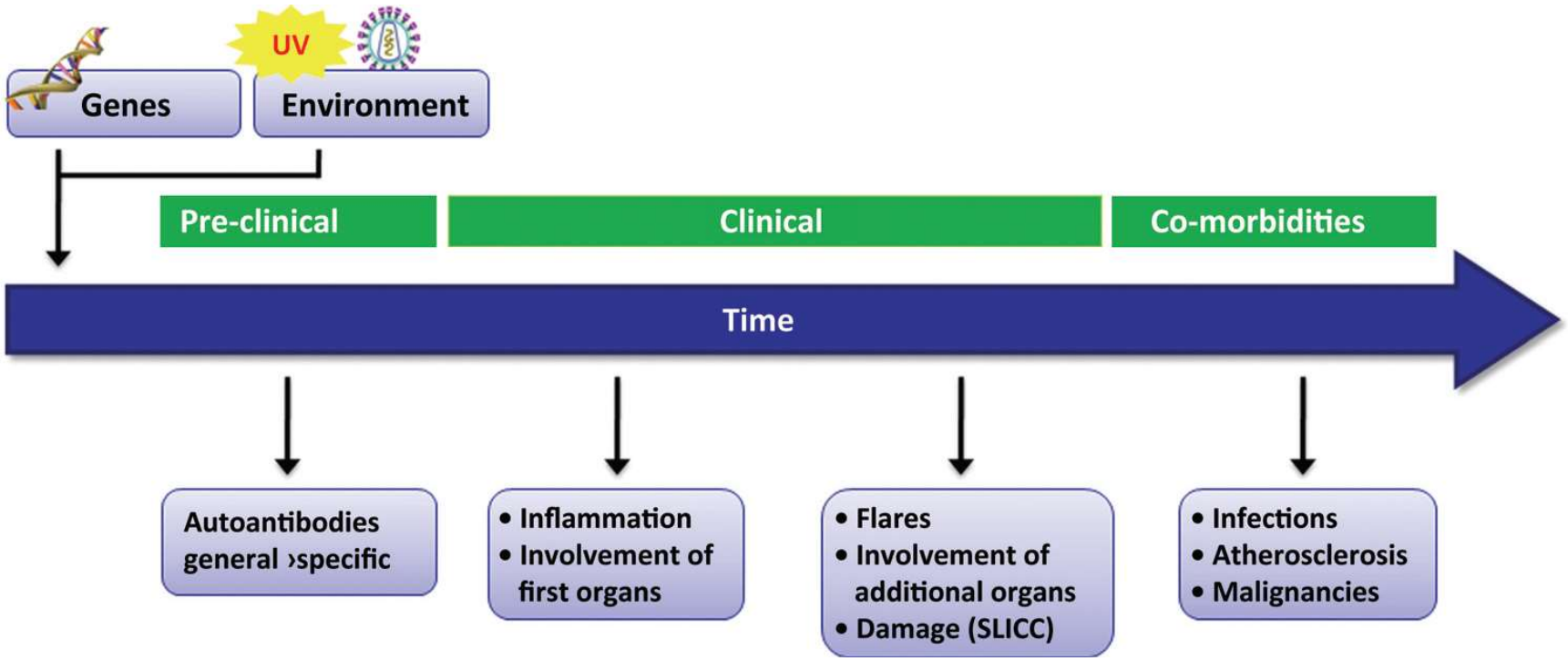
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

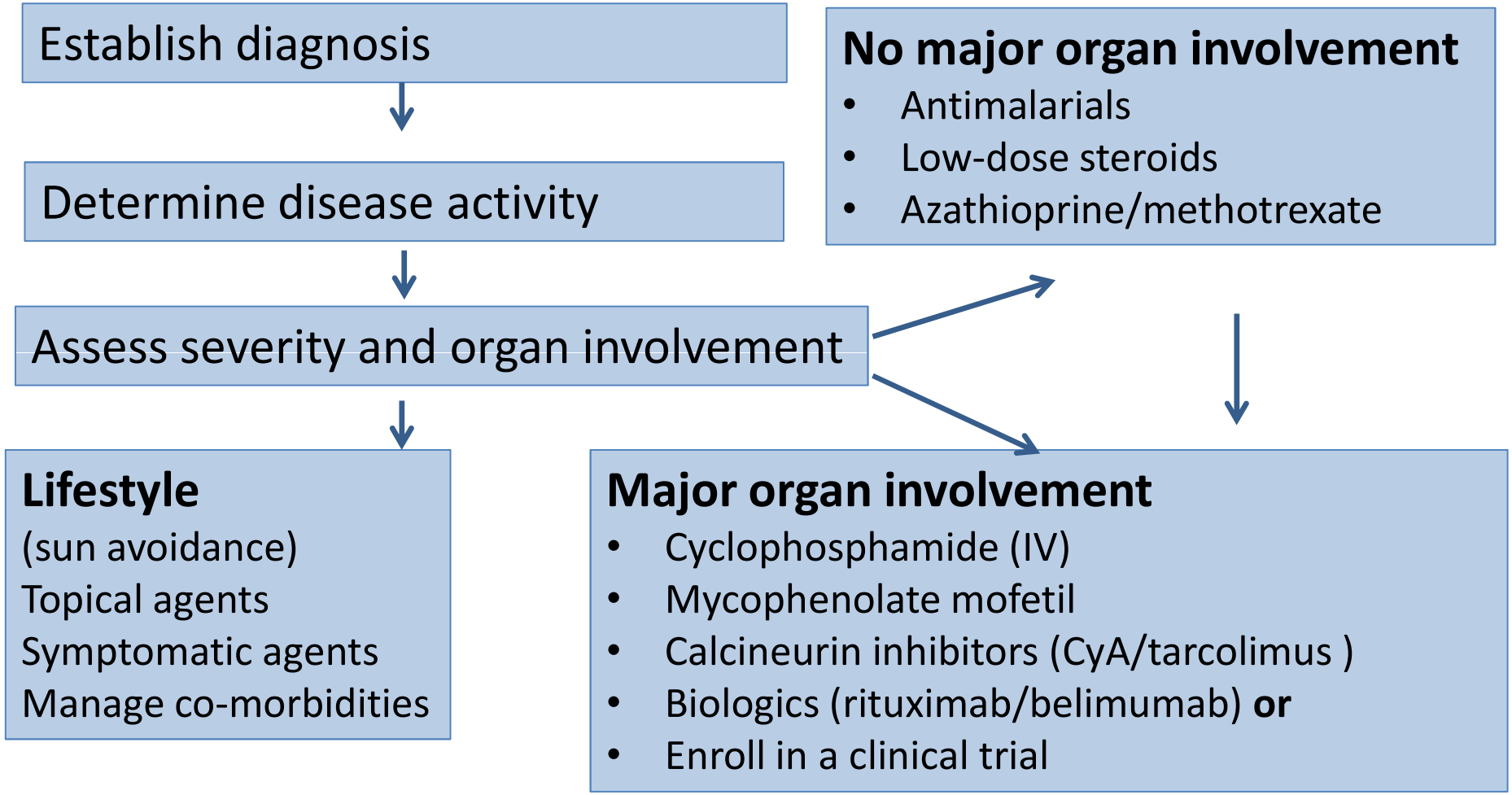
Total score:

Natural history of SLE



*Ann Rheum Dis 2010;**69**:1603–11*

Overview of management of SLE



Overview of the management of systemic lupus erythematosus -John A Reynolds, Ian N Bruce
Issue 2 (Topical Reviews Series 7) Spring 2013

Treatment of SLE

- No permanent cure for SLE: treatment relieves symptoms

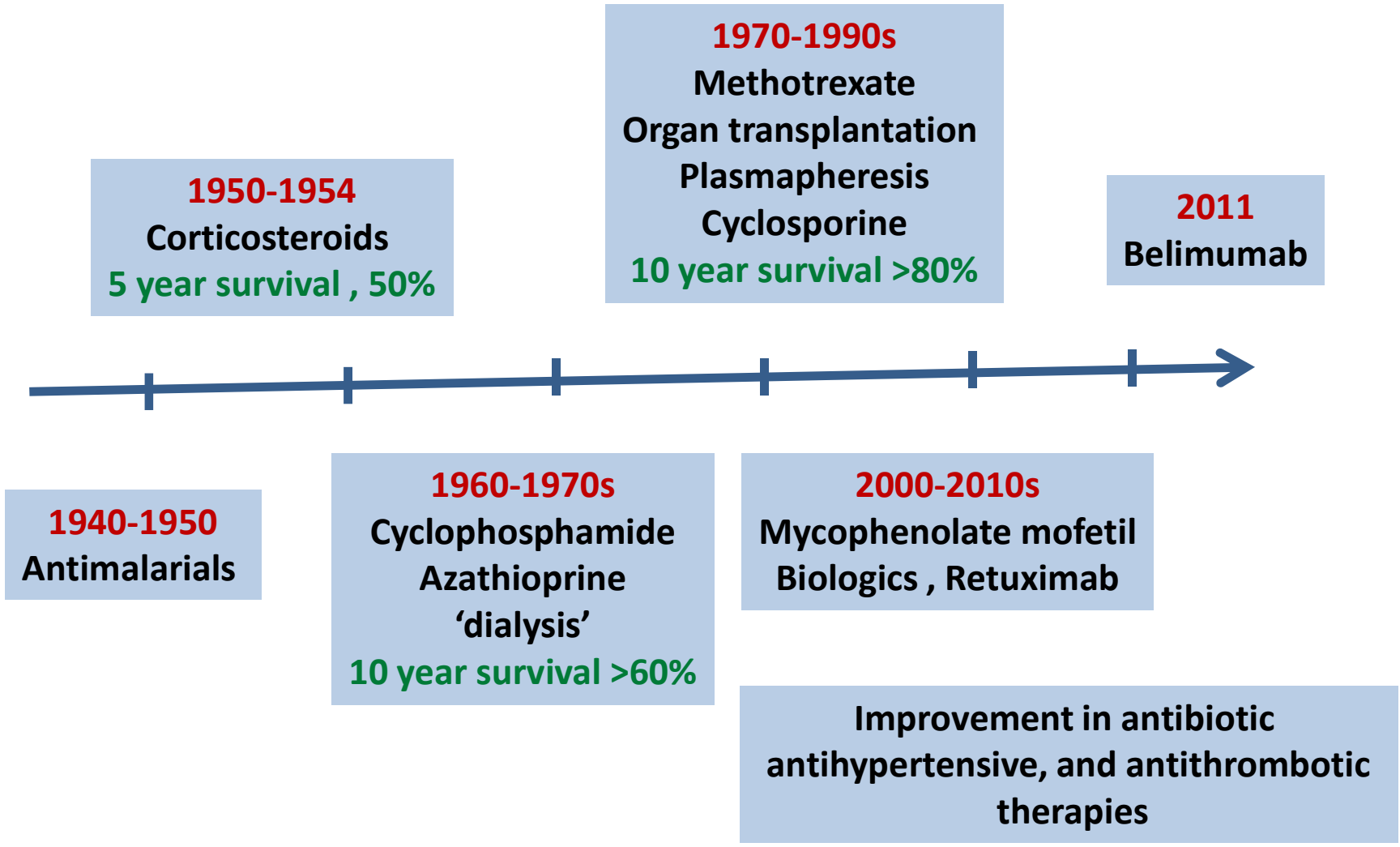
❖ **NSAIDs** (nonsteroidal anti-inflammatory drugs): Reduce inflammation and pain

❖ **Corticosteroids**
  - Reduce inflammation
  - Used after significant organ damage

❖ **Antimalarial Drugs**
  - Hydroxychloroquine (Plaquenil), chloroquinone (Aralen)
  - Reduces inflammation, protects against organ damage
  - Used for skin symptoms, joint pain

❖ **DMARDs (disease-modifying antirhematic drugs)**
  - Belimumab (Benlysta), rituximab (Rituxan)
  - Methotrexate, azathioprine and mycophenelate mofetil

Mortality and Treatment



Adapted from Manzi S ,ACR 2012

Hydroxychloroquine

- Reduction in flares
- Reduction in lipids
- Reduction in thrombosis
- Reduction in organ damage
- Improved survival
- Triples mycophenolate response
- Prevents seizure
- Reduction in CHB in neonatal lupus

Vitamin D

Improved vitamin D level positively affects:

- Disease activity
- Urine protein/Cr
- Systolic blood pressure

Low vitamin D is associated with venous thrombosis

Morbidity and mortality in SLE

- Mortality Rate in SLE is 2–3 x higher than general population

- Risks of death increased in females, Blacks, and younger-onset patients

Most common causes of death in SLE patients

- ❖ Heart disease and stroke
- ❖ Hematologic malignancies and lung cancer
- ❖ Infections
- ❖ Renal disease

Morbidity in SLE

Table – Prevention and screening strategies for 4 important aspects of SLE

Comorbidity or complication	Strategy
Cardiovascular disease	Maintain vigilance (eg, pursue further testing in patients who have atypical chest pain for which the causes are unknown). Screen for and address traditional risk factors yearly, including cigarette smoking status, blood pressure, BMI, diabetes mellitus, and serum lipid levels (eg, total cholesterol, HDL, LDL, and triglycerides). Inform patients about increased risk.
Infection	Ensure that all patients are up-to-date on routine vaccinations. Vaccinate all immunosuppressed patients with an inactivated influenza vaccine yearly, as well as a pneumococcal vaccine.
Osteoporosis	Order BMD testing for patients who are at risk for osteoporosis, including those older than 65 years, those older than 60 years with a risk factor, and all those who are starting corticosteroid therapy. Add antiresorptive or anabolic therapy for eligible patients with significant osteopenia while receiving corticosteroids, those with osteoporosis, and those with a history of fragility fracture.
Cancer	Maintain vigilance for cancers not routinely screened for (eg, lymphoproliferative malignancies). Ensure that routine cancer screening is up-to-date.

SLE, systemic lupus erythematosus; BMI, body mass index; BMD, bone mineral density; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Conclusions “take home massages”

- SLE is a heterogeneous multisystem disease which varies among races and ethnicities
- SLE pathogenesis is complex with dysregulation of multiple arms of the immune system
- Early lupus diagnosis and disease monitoring remains a challenge for treating physicians

Thank you