# Systemic Lupus Erythematosus

## Objectives :

- ★ What is Systemic lupus erythematosus (SLE)
- ★ What are the clinical features of Systemic lupus erythematosus (SLE)
- ★ How to diagnose Systemic lupus erythematosus?
- ★ How to treat Systemic lupus erythematosus?
- ★ Prognosis of SLE

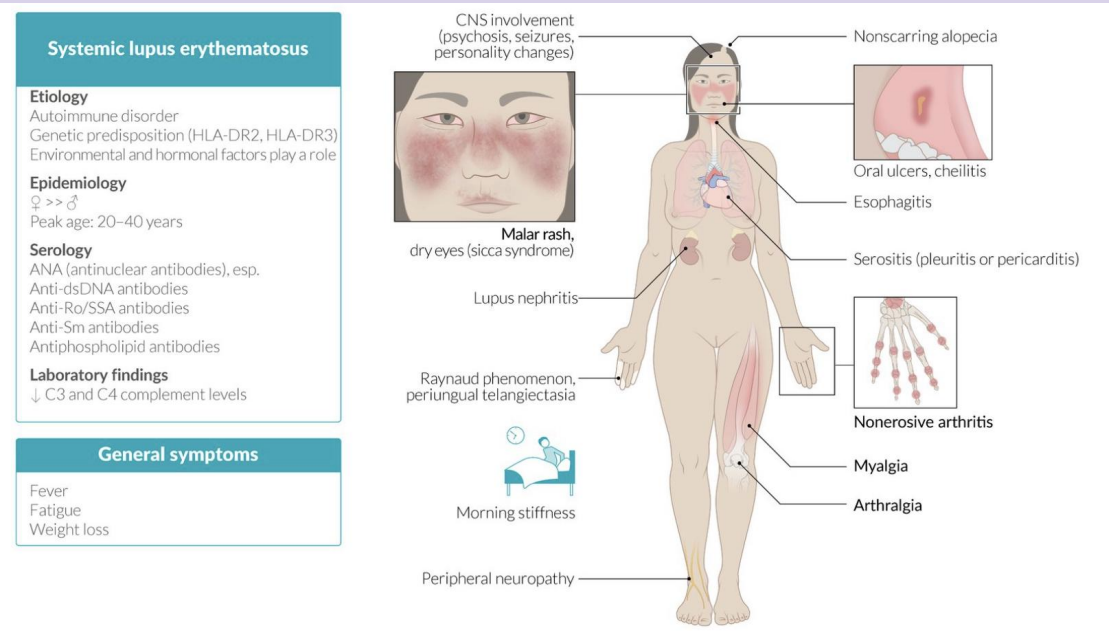
Editing file

**Color index**

Original text
Females slides
Males slides
Doctor's notes [438]
Doctor's notes [439]
Text book
Important
Golden notes
Extra

# Lecture Outline “AMBOSS” :

**Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects women of childbearing age. The exact cause is still unknown, but hormonal and immunological features as well as genetic predisposition are considered likely etiological factors. The presentation of the disease is variable but usually characterized by phases of remission and relapse. Symptoms can range from mild localized symptoms to life-threatening systemic disease. SLE can affect any organ, but typical findings include arthritis, a malar rash (facial butterfly rash), and constitutional symptoms such as fever and fatigue. The diagnosis of SLE is based on clinical findings and is further supported by antibody tests, particularly for ANA, anti-dsDNA, and anti-Sm. Management consists of supportive measures, such as avoiding sun exposure, and medication adapted to disease severity. Long-term pharmacotherapy typically consists of hydroxychloroquine, which has been shown to reduce flares and decrease mortality. For acute flares, glucocorticoids are given as induction therapy, with dose and treatment duration adapted to the severity of the flares. In severe cases, additional immunosuppressants (e.g., mycophenolate, azathioprine) may be given. Cardiovascular, neurological, and renal disease (lupus nephritis), together with infections, are the main causes of death in patients with SLE.**



# SLE

## Definition

Chronic, multisystem inflammatory disease characterized by autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.

## ◀ Background

- First written description in13th century (Rogerius) named it lupus (Latin for wolf) as cutaneous similar to a wolf bite.
- Osler recognized systemic features without skin .
- Diagnosis with (LE) cells in 1948. Not used any more
- Anti-DNA was described in 1959

## ◀ Epidemiology

- women of childbearing age

**Internationally**

- Variable prevalence
- Denmark (21.7/100,000)
- Britain, 12 cases per 100,000.
- India prevalence (3.2/100,000)
- 39 cases per 100,000 population in Sweden.

VS

**Locally**

2 cases of SLE among 10,372 studied (prevalence of 19.28 per 100,000).

## ◀ Pathophysiology

- The pathophysiology involves autoantibody production, deposition of immune complexes, complement activation, and accompanying tissue destruction/vasculitis.
- **Disturbances in the immune system:**

**Defects in immune cell tolerance leading to:**

➔ Production of **autoantibodies targeting** antigens located in **nuclei**, **cytoplasm**, on cell surfaces, and in plasma proteins

Cell-mediated autoimmunity also play part.

**High ratio of CD4+ to CD8+ T cells.**

**Autoantibodies**

➔ Mostly immune complex formation (e.g kidney)

➔ Direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).

Tissue damage follows

# SLE

## ◀ Aetiology

**Specific cause(s) of SLE is unknown.** Multiple factors play a role in the etiology of SLE:

01

### Environmental

- worldwide variability of prevalence the disease (black in africa and US).
- influence of environmental factors on the course of the disease, eg: **Ultraviolet light**, viruses (e.g. **EBV**), drugs cause or exacerbate, silica dust, cigarette smoking, alfalfa sprouts.

02

### Genetic predisposition:

Multitude of genetic associations suggests a complex genetic predisposition.

- Concordance rate in monozygotic twins is 25-70%.
- **If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250.**
- Relatives have a high prevalence of other autoimmune diseases.
- **HLA-DR2** and **HLA-DR3** and other HLA genes occur more often in SLE than in the general population.
- null complement alleles and **congenital deficiencies of complement** ( **C4**, **C2**, **C1q** and other early components) are associated with an increased risk of SLE.

03

### Female to male rations and Hormonal factors

- **F:M ratio** of prevalence in different age groups:
  - ➔ Children: 3:1
  - ➔ Adults: 10-15:1
  - ➔ Elderly: approximately 8:1 ( Ratio ↓ Due to testosterone decline)
  - ➔ **So, it affect females more than males.**

- **Age at onset :**
  - ➔ 65%: between **16 and 55 (Reproductive age)**.
  - ➔ 20%: before age 16.
  - ➔ 15%: after age 55 .

| SLE in Saudi arabia | | |
|---|---|---|
| **Sex** | **Number** | **Total** |
| Male | 58 | 9.3 |
| Female | 566 | 90.7 |
| Total | 624 | 100 |

- Higher prevalence in men with **Klinefelter disease**, their extra X chromosome increases their susceptibility.
- Exogenous estrogen and exacerbations of SLE (oral contraceptives may lead to SLE exacerbation) basically any hyperestrogenic state.
- Men at all ages have the same risk of disease as women who are prepubertal or postmenopausal ( The higher incidence in premenopausal women and males with Klinefelter's (XXY) suggests an estrogen hormonal effect )
- **Males do not have an age-related peak in incidence.**

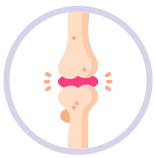
04

### Racial and geography:

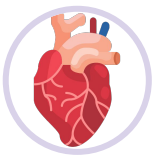
- In USA: 2.5- to 6-fold higher prevalence in African American women than in white women. But it occurs infrequently in Blacks in Africa . (black in africa has less SLE than black in US, because they went to environment that have different factors Such as urban society, different or not natural food.. etc )
- Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians.
- More common in urban than rural areas .
- In New Zealand, 50 per 100,000 Polynesians, but only 14.6 cases per 100,000 in the whites.
- In France, more common among immigrants from Spain, Portugal, North Africa, and Italy

# SLE

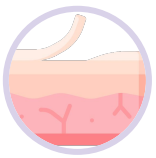
## ◀ Organ involvement in SLE:



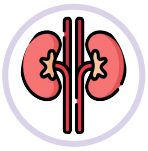
**Joints 90%**



**Pleuro-peri cardial 60%**



**Skin**
Rashes: 70%
Discoid lesions: 30%
Alopecia: 40%

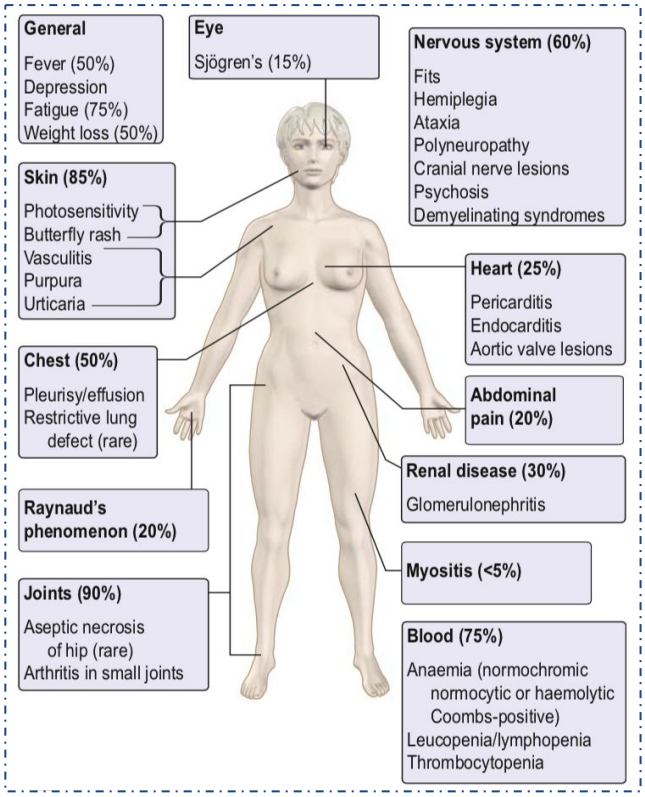


**Kidney 50%**

**Raynaud's 20%** (secondary)

**CNS 15%** Psychosis, convulsions

**Mucous membrane 15%**




## ◀ Other organs:

| | |
|---|---|
| Lung | recurrent pleurisy, pleural effusion bilateral ,pleuritic pain (serositis) are most common manifestation, pneumonitis and atelectasis are seen. some pt develop restrictive lung defect. |
| Eyes | retinal vasculitis can cause infarct and hemorrhage, there may be episcleritis, conjunctivitis, or optic neuritis, but blindness is uncommon. |
| GI | mesenteric vasculitis can produce inflammatory lesions involving the small bowel, liver involvement and pancreatitis are uncommon |
| Heart | pericarditis with small pericardial effusion is common. a mild myocarditis also occur giving raise to arrhythmias. increase frequency of IHD and stroke in SLE pt due to altered levels of common risk factors. |

## ◀ Primary Central Nervous System Lupus

The pathogenic mechanism for cerebral lupus is complex. Lesions may be due to vasculitis or immune complex deposition, thrombosis or non-inflammatory microvasculopathy. In pt with cerebral lupus infection should be excluded or treat in parallel with CS and immunosuppression.

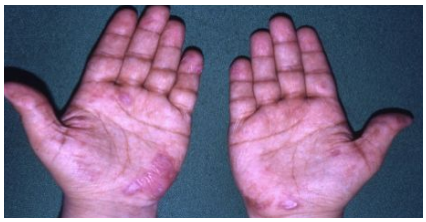
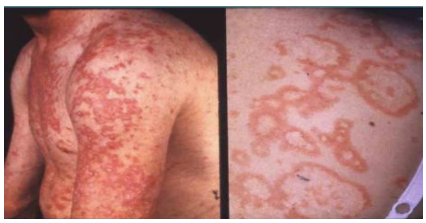
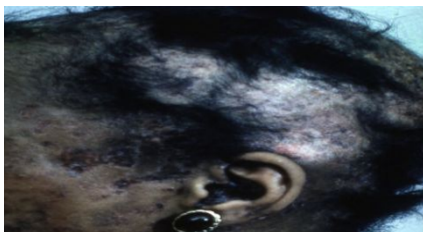
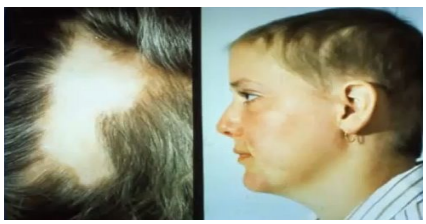
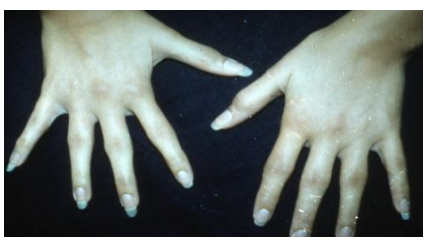
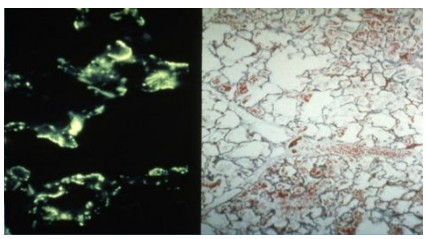
**Neurologic Signs or Symptoms:**

1. **Meninges**
   Headache, meningismus
2. **Cerebrum**
   Dementia, strokes, subarachnoid hemorrhages
3. **Cerebellum**
   Ataxia
4. **Spine**
   Paraparesis, MS-like disorder
5. **Cranial and peripheral nerves**
   Cranial and peripheral sensory, motor neuropathies, mononeuritis multiplex
6. **Other**
   migraine,other headaches seizures,tremor, rigidity, chorea, SIADH, myasthenia gravis & Guillain-Barre syndrome

# Systemic Lupus Erythematosus

## ◀ Clinical features:

- arthralgia and rashes are the most common clinical feature, and renal and cerebral disease are the most serious problems

| | | |
|---|---|---|
| **Bullous rash** | |  |
| **Subacute cutaneous lupus erythematosus** | associated with **Anti-SSA/RO** & neonatal lupus. **leads to complete heart block** in the fetus (2%) |  |
| **Chronic discoid rash**<br><br>**Discoid scarring alopecia** (Irreversible) | Hits deeper & destroys the hair follicles (Hair will never grow again) and pigment cells causing post inflammatory hypopigmentation or hyperpigmentation. Ears are the classic site for discoid lupus. |  |
| **Alopecia** | usually non scarring, goes back to normal once you treat the patient. the secret is to treat early |  |
| **Externally not distinguishable from RA** | X-ray shows non erosive correctable deformity |  |
| **Lupus in the lung capillaries (Emergency)** | inflammation of the vessels → break in the walls of the vessels → blood comes out → Pulmonary alveolar hemorrhage (mortality is 50%) |  |

# ◀ SLE – Presenting and Prevalent Symptoms:

➔ **ARA Criteria** [n = 624] SAUDI ARABIA

| ARA Criteria | +ve at presentation n (%) | +ve on * follow up n (%) | Total prevalent (%) n |
|---|---|---|---|
| Malar rash | 265 (42.5) | 34(5.4) | 299(47.9) |
| Discoid rash | 99 (15.9) | 11(1.8) | 110(17.6) |
| Photosensitivity | 165 (26.4) | 26(4.2) | 191(30.6) |
| Oral ulcer | 223 (35.7) | 21(3.4) | 244(39.1) |
| Arthritis | 454 (72.8) | 7(1.1) | 461(73.9) |
| Serositis | 82 (13.1) | 89(14.3) | 171(27.4) |
| Renal disorder | 281(45) | 18(2.9) | 299(47.9) |
| Neurological disorder | 98(15.8) | 20 (3.2) | 172(27.6) |
| Hematological disorder | 505 (80.9) | 31(4.9) | 536(85.9) |
| Immunological disorder | 470(75.3) | 30 (4.8) | 500(80.9) |
| ANA | 622(99.7) | 0 | 622(99.7) |

➔ **Other symptoms** (n= 624):

- constitutional symptoms:
  - **Fever** (30.6)[2]: one of the DDx of fever with unknown origin is SLE
  - Weight Loss (23.1)[2]
  - Fatigue (42.5)
- Arthralgia (86.9)
- Raynaud's phenomenon (8.7)[1]
- Alopecia (47.6) (Can be acute or chronic)
- Lymphadenopathy (20.0)[2]
- DVT (7.4)
- Ascites (8.9)
- Hepatomegaly (3.2)
- Splenomegaly (2.6)
- Hepatosplenomegaly (6.1)
- Genital ulcers (1.4)
- HTN (28.4)
- Myalgia (6.6)
- Pancytopenia (12.2)
- Pleuritis (15.8)
- Pericarditis (20.7)
- Pulmonary symptoms (28.0)
- Gastrointestinal symptoms (38.6)

1. secondary Raynaud's phenomenon associated with SLE and other AICTDs, features that favour secondary Raynaud's:
   - age at onset over 25 years, absence of family history, occurs in male.
2. fever, weight loss, and mild lymphadenopathy are common in exacerbation

# Diagnostic criteria of SLE

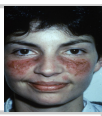
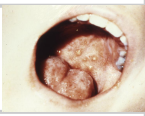


Dr. you're only involved in patient's diagnosis so focus on this criteria.

## ◀ Clinical presentation, and Diagnostic Criterion.

➔ **ANA is needed to diagnose:** early criterion, found in 95%-99% of cases. A negative ANA is extremely sensitive for SLE.

➔ You need to have **at least 4** of the following: (the more you get the more definite the diagnosis is)

| | |
|---|---|
| **Malar rash** Butterfly rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. Acute → resolves if treatment is started early.  |
| **Discoid rash** | Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions. it is a Chronic disfiguring rash, affect deeper layers. |
| **Photosensitivity** | Skin rash as a result of unusual (abnormal) reaction to sunlight, by patient history or physician observation. |
| **Oral ulcers** | Oral or nasopharyngeal ulceration, usually **painless** (unlike the ones present in behcet's disease), observed by physician. may become secondarily infected and painful.  |
| **Arthritis** | **Nonerosive** (but maybe deforming) arthritis involving 2 or more peripheral joints, usually symmetrical. characterized by tenderness, swelling, or effusion. Arthritis here is "**Nonerosive**" unlike Rheumatoid arthritis |
| **Serositis** | **A. Pleuritis:** convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion<br>**B. Pericarditis:** documented by ECG or rub or evidence of pericardial effusion.<br>**C. Peritonitis** |
| **Renal disorder** one of the most serious signs | typical renal lesion is a proliferative glomerulonephritis, usually affect around 50% of patients. characterized by:<br>A. **Persistent proteinuria:** >0.5 g/day or >3+ if quantitation not performed<br>B. **Cellular casts:** may be red cell, hemoglobin, granular, tubular, or mixed<br>all SLE pt should have regular screening of urine for blood and protein. |
| **Neurologic disorder** | • **Psychosis or Seizures** (e.g. fatigue, headache, and poor concentration) **:** in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance<br>• **Cerebral lupus feature:** visual hallucination, chorea, organic psychosis, transverse myelitis, and lymphocytic meningitis. |
| **Hematologic disorder (Blood)** | A. **Hemolytic anemia** with reticulocytosis ( less common than other hematologic disorders).<br>B. **Leukopenia** less than **4,000/mm$^3$** total on 2 or more occasions<br>C. **Lymphopenia** less than **1,500/mm$^3$** on 2 or more occasions( the degree of lymphopenia is a good guide to disease activity)<br>D. **Thrombocytopenia** less than **100,000/mm$^3$** in the absence of offending drugs<br>E. Neutropenia. |
| **Immunologic disorder either:** | **A. +ve antiphospholipid antibodies by either:**<br>**a.** An abnormal serum level of IgG or IgM anticardiolipin antibodies.<br>**b.** A positive test result for lupus anticoagulant using a standard method.<br>**c.** A false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test<br>**B. Anti-DNA:** antibody to native DNA in abnormal titer Highly associated with lupus nephritis,+ it correlates with disease activity so it's used for **monitoring** **(Dr. I like to have it . If not ,it won't stop me from diagnosing SLE)**<br>**C. Anti-Sm:** presence of antibody to Smith nuclear antigen |
| **Antinuclear antibody (ANA)** | • An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome<br>• **condition in which ANAs are elevated:** SLE, RA, Scleroderma, Sjögren syndrome, Mixed connective tissue disease, Polymyositis dermatomyositis, Drug-induced lupus. |

# Diagnostic criteria of SLE *(cont.)*

## ◀ SLICC PI Classification Criteria for SLE

(dr: you don't need to know this criteria, stick to the previous one (page 7 on the team)). It is used in clinical studies not practice

**SLICC PI: DR. MICHELLE PETRI**

- SLICC classification criteria for Systemic Lupus Erythematosus used in studies.
- New Investigator: Dr. Ana-Maria Orbai Funding Source: National Institutes of Health
- Seventeen criteria were identified in a very time-consuming and laborious process which involved the consensus diagnosis of over 700 patient scenarios, the reduction in the number of potential variables by extensive logistic regression analyses, the use of recursive partitioning to derive classification rules and the refinement of the rules when agreement was not achieved. In a second step, another set of over 600 patient scenarios was used to validate the criteria. This process took well over a decade from its conception to publication.

**The SLICC criteria for SLE classification requires:**

Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion

**Or**

Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies, proven by biopsy.

| Clinical Criteria | Immunological Criteria |
|---|---|
| Acute cutaneous lupus | ANA above laboratory reference range |
| Chronic cutaneous lupus | |
| Oral ulcers: palate | Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory |
| Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) | |
| Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and thirty minutes or more of morning stiffness. | Anti-Sm |
| Serositis | Antiphospholipid antibody: any of the following |
| Renal | |
| Neurologic | Low complement (C1q, C2, C4) |
| Hemolytic anemia | |
| Leukopenia (< 4000/mm3 at least once) | Direct Coombs test in the absence of hemolytic anemia |
| Thrombocytopenia (<100,000/mm3) at least once | |

# Diagnostic criteria of SLE *(cont.)*

## ◀ ACR and EULAR Classification Criteria for SLE

(dr: you don't need to know this criteria, stick to the first one (page 7 on the team))

All patients classified as having systemic lupus erythematosus **must have a serum titer of antinuclear antibodies of at least 1:80 on human epithelial-2-positive cells or an equivalent positive test**. In addition, a patient must tally **at least 10 points from these criteria**. A criterion is not counted if it has a more likely explanation than SLE. Occurence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts.

### New ACR and EULAR criteria for classification of SLE

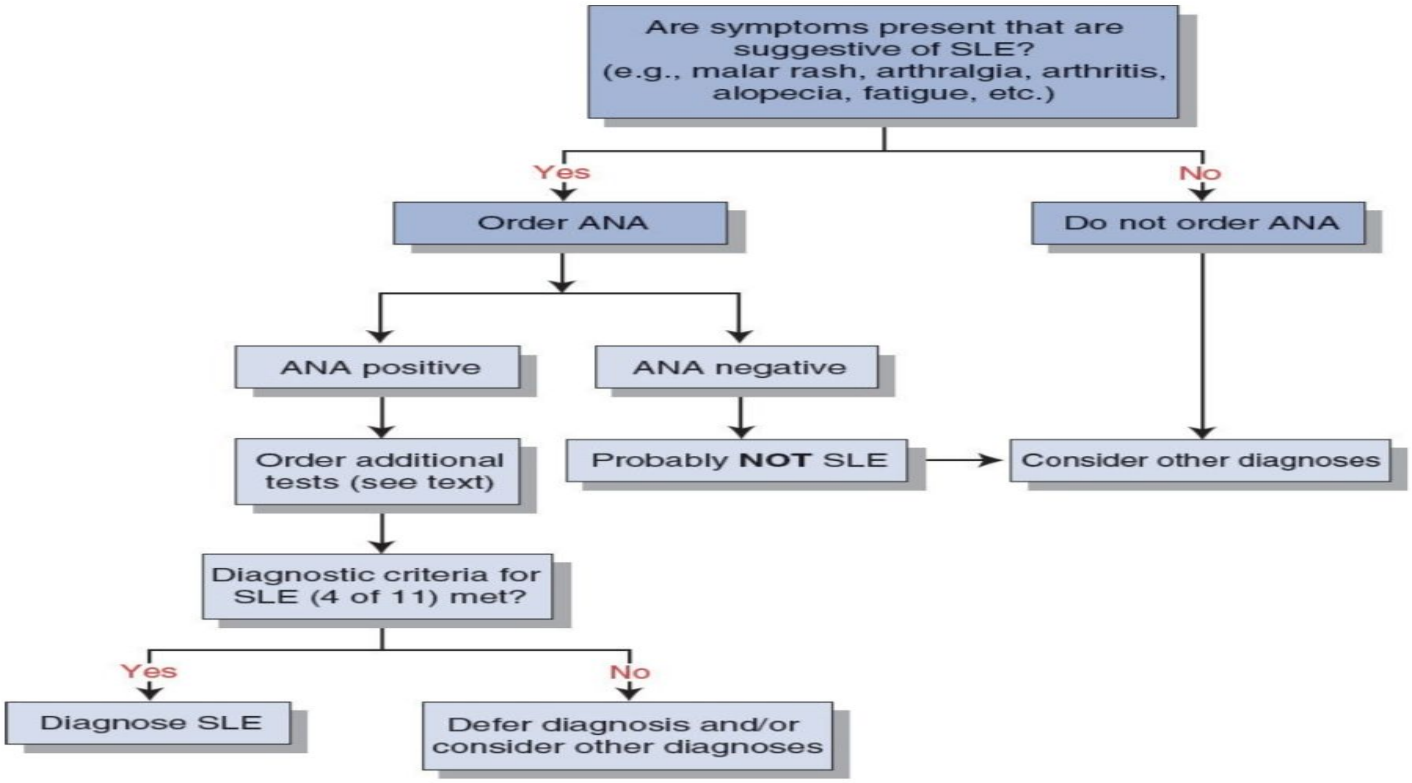
All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2-positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

| Clinical domains | Points |
|---|---|
| ***Constitutional domain*** | |
| Fever | 2 |
| ***Cutaneous domain*** | |
| Nonscarring alopecia | 2 |
| Oral ulcers | 2 |
| Subacute cutaneous or discoid lupus | 4 |
| Acute cutaneous lupus | 6 |
| ***Arthritis domain*** | |
| Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness | 6 |
| ***Neurologic domain*** | |
| Delirium | 2 |
| Psychosis | 3 |
| Seizure | 5 |
| ***Serositis domain*** | |
| Pleural or pericardial effusion | 5 |
| Acute pericarditis | 6 |
| ***Hematologic domain*** | |
| Leukopenia | 3 |
| Thrombocytopenia | 4 |
| Autoimmune hemolysis | 4 |
| ***Renal domain*** | |
| Proteinuria >0.5g/24 hr | 4 |
| Class II or V lupus nephritis | 8 |
| Class III or IV lupus nephritis | 10 |

| Immunologic domains | Points |
|---|---|
| ***Antiphospholipid antibody domain*** | |
| Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant | 2 |
| ***Complement proteins domain*** | |
| Low C3 or low C4 | 3 |
| Low C3 and low C4 | 4 |
| ***Highly specific antibodies domain*** | |
| Anti-dsDNA antibody | 6 |
| Anti-Smith antibody | 6 |

# Systemic Lupus Erythematosus

## ◀ SLE approach :




## ◀ Antibodies Associated with Rheumatic Diseases:

| Antibodies to: | Percentages of patients | Antibodies to: | Percentages of patients |
|---|---|---|---|
| **Native DNA** | SLE: 50% - 60% | **Nucleolar antigens** | Scleroderma: 40% - 50% |
| **Sm antigen** | SLE: 30% | **Scl-70** | Scleroderma: 10% - 20% |
| **Histones** | **Drug-induced SLE:** 95% SLE: ≤ 60% Rheumatoid arthritis: 20% | **PM-1** | Polymyositis: 50% Dermatomyositis: 10% |
| **SS-A** | Sjogren's syndrome: 70% SLE: 30% - 40% Scleroderma and mixed connective tissue disease: frequency and titers low | **RNP** | Mixed connective tissue disease: 95% - 100% SLE: 30% at low titers Scleroderma: 10% - 20% |
| **SS-B** | Sjogren's syndrome: 60% SLE: 15% | **Centromere antigens** | CREST: 80% - 90% |

# Systemic Lupus Erythematosus

## ◀ Investigations

| | |
|---|---|
| **Blood count** | • Normochromic, normocytic anaemia or autoimmune hemolytic anemia<br>• Neutropenia<br>• Lymphopenia<br>• leucopenia<br>• thrombocytopenia |
| **ESR and CRP** | • ESR: raised in proportion to the disease activity. **A raised ESR, leukopenia and lymphopenia are typical of active SLE**<br>• CRP: usually normal unless the patient has a coexistent infection (lupus pleuritis or peritonitis) or in the presence of serositis. |
| **Urea and creatinine** | • Only rise when renal disease is advanced.<br>• Low serum albumin or high urine protein/creatinine ratio → early indicators of lupus nephritis. |
| **Serum** | **Complement C3 and C4 levels: reduced** in active disease. due to complement consumption. Maybe the result of inherited complement deficiency (C1, C2 and C4) |
| | **Autoantibodies:**<br>A. **ANA:** Sensitive but not specific<br>B. **Anti-ds DNA** (in 70%): highly specific (but not sensitive)<br>C. **Anti-Smith** (in 30%): very specific (but not sensitive)<br>D. **Antiphospholipid antibodies** (in 25% to 40%)<br>E. **Antihistone** (in 70%) are present in >95% of cases of **drug-induced lupus**. If negative, drug-induced lupus can be excluded.<br>F. **Ro (SS-A) and La (SS-B)** ( in 15% to 35%). **Associated with:**<br>A. Sjögren syndrome<br>B. Subacute cutaneous SLE<br>C. complement deficiency (C2 and C4)<br>D. ANA-negative lupus<br>E. Neonatal lupus (with congenital heart block)<br>**Markers that correlate with disease activity:**<br>1) Anti-dsDNA<br>2) Complement levels C3 and C4 (Drops in acute lupus flares) |
| **Histology** | Characteristic deposition of IgG and complement in kidney or skin biopsies |
| **imaging** | CT of brain sometimes show infarcts or hemorrhage with evidence of cerebral atrophy<br>MRI can detect lesions in white matter |

## ◀ Drug Induced Lupus

**(consider before diagnosing native lupus) :**

- Sex ratios are nearly equal.
- Nephritis and CNS not common. (Because it's usually diagnosed early and isn't due to an intrinsic disease as in SLE)
- No anti-native DNA or hypocomplementemia.
- Resolution on **discontinuation of drug**. Some cases take 6 months to resolve, and some require treatment with immunosuppressive drugs such as corticosteroids.

# Systemic Lupus Erythematosus

## ◀ Drugs associated with lupus erythematosus

- Drug induced lupus typically does not affect the CNS and kidneys the way that SLE does.

| Definite association | Possible association | Unlikely Association: |
|---|---|---|
| • Chlorpromazine(antipsychotic)<br>• Methyldopa (antihypertensive)<br>• Hydralazine(antihypertensive)<br>• Procainamide (antiarrhythmic)<br>• Isoniazid (antibiotic)<br>• Quinidine (antiarrhythmic). | Beta blockers, Methimazole, Captopril, Nitrofurantoin, Carbamazepine, Penicillamine, Cimetidine, Phenytoin, Ethosuximide, Propylthiouracil, Hydrazines, Sulfasalazine, Levodopa, Sulfonamides, Lithium, Trimethadione | Allopurinol, Penicillin, Chlorthalidone, Phenylbutazone, Gold salts, Reserpine, Griseofulvin, Streptomycin, Methysergide, Tetracyclines, Oral contraceptives |

My Two HIPS: Methyldopa/Minocycline; TNF-α inhibitors; Hydralazine; Isoniazid; Procainamide/Phenytoin; Sulfa drug

## ◀ Treatment of SLE

➔ **Goal of therapy:**

- ensure long-term survival
- minimize drug toxicity
- achieve the lowest possible disease activity
- improve quality of life
- prevent organ damage
- educate patients on their role in disease management.

**Treat depending on the organ system(s) involved (we treat according to symptoms and signs):**

**Mild to moderate disease:** restricted to skin, musculoskeletal, and serositis. Managed with Analgesic.

- ➢ NSAIDs (Arthralgia, arthritis, fever and serositis all respond well to standard doses of NSAIDs)
- ➢ hydroxychloroquine (antimalaria, help in mild skin disease, fatigue and arthralgias that cannot be controlled with NSAIDs, but pt require regular eye chicks for potential retinal toxicity)
- ➢ Topical/Local corticosteroid effective and widely used in cutaneous lupus

**Life-threatening disease:** for the treatment of **renal, CNS, and cardiac involvement** or flares.

- ➢ **High-dose corticosteroids and immunosuppressants**
- ➢ immunosuppressant drugs:(maintain remission)
  - **Cyclophosphamide**: was most commonly used, may cause hemorrhagic cystitis, Cyclophosphamide is an example of immunosuppressants that we **try to avoid in patients in productive age**. If we need to give it, it is given at lower doses, then switch to mycophenolate.
  - **Mycophenolate mofetil**: has less side effects, it is CI in pregnancy
  - **Azathioprine**
  - **Biological therapy (Rituximab and Belimumab):** monoclonal antibodies acting against B lymphocytes
  - **Tacrolimus**
  - Anti-interferon agents.
- ➢ **Other treatments:**
  - Plasma exchange for TTP or diffuse alveolar hemorrhage
  - Intravenous immunoglobulin for severe steroid non-responsive thrombocytopenia.

## ◀ Treatment *(cont.)*

**Treat depending on the organ system(s) involved *(cont.)*:**

**Maintenance therapy:** a typical maintenance regimen is: oral CS in a dose of 40-60 mg daily gradually reducing to 10-15 or less by 3 months. azathioprine, methotrexate, or MMF.

- the long term aim is to continue the lowest dose of CS and immunosuppressant to maintain remission.
- pt with SLE and antiphospholipid antibody syndrome, who had previous thrombosis, require lifelong warfarin therapy.

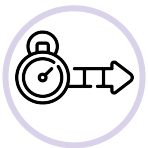
**General considerations: Prevention[1]**

- This isn't primary prevention, we can't prevent SLE bc we don't have major control over the genetic factors predisposing to SLE nor the environment and the other factors
- Avoid uv light and sun (sunscreening)
- Antimalarial (Hydroxychloroquine and chloroquine) to prevent **relapses**. (For those who already got Lupus to prevent relapses, not just have +ve ANA)
- Treat hypertension and dyslipidemias .

## ◀ Remission

**After appropriate therapy, many patients go into a clinical remission requiring no treatment.**
a long-term follow-up of 667 patients noted:

≈25 % had at least one treatment-free clinical remission lasting for at least one year.



The mean duration of remission was **4.6 years** ( underestimated since one-half of the patients were still in remission at the end of follow-up).

A long history of SLE or the presence of renal or neuropsychiatric disease did not preclude remission

## ◀ Pregnancy and SLE

- **Fertility**: usually normal except in severe disease and there is no major contraindication to pregnancy. Recurrent miscarriages can occur, **especially in women with anti-phospholipid antibodies**.
- **Medications:** should be reviewed. Mycophenolate should be stopped whereas azathioprine, hydroxychloroquine and low-dose oral corticosteroids are safe. Hypertension must be controlled.

# Systemic Lupus Erythematosus

## ◀ Prognosis

**Poor prognostic factors for survival in SLE include :**

01 **Renal disease**: especially diffuse proliferative glomerulonephritis (Especially class 3 and **4**). Renal involvement is one of the main determinants of prognosis

02 **Hypertension:** Because it affects the kidney.

03 **Central nervous system (CNS) disease**

04 **low education** (poor compliance)

05 **Poor socioeconomic status** (inadequate access to medical care ) insignificant in our society.

06 **Black race** ( low socioeconomic status) insignificant in our society.

07 **Presence of antiphospholipid antibodies**: increase the risk for thrombosis in CNS, kidney and lungs.
**Antiphospholipid syndrome:** thrombosis (arterial or venous) and/or recurrent miscarriages and who also have persistently positive blood tests for antiphospholipid antibodies (aPL).

- Detected by:
  - anticardiolipin test
  - lupus anticoagulant test
  - anti-β2-glycoprotein I test

A persistently positive test (i.e. positive on at least two occasions, ≥12 weeks apart) in one or more of these assays is needed to diagnose APS.

- Clinical features:
  - Thrombocytopenia, Chorea, migraine and epilepsy, Valvular heart disease, Cutaneous manifestations (e.g. livedo reticularis), Positive Coombs test, Renal impairment due to ischaemia in the small renal vessels.
- Treatment:
  - Warfarin (do not use NOAC)
  - Pregnant women with APS are given oral aspirin and subcutaneous heparin from early in gestation to reduce chances of miscarriage.
  - In case of high IgG aPL: Aspirin or clopidogril.

08 **High overall disease activity:** SLE patients have an increased long-term risk of developing some cancers, especially lymphoma.

09 **Male sex:** Men show similar frequency of renal, skin, arthritis, and CNS as women, But less photosensitivity, more serositis, an older age at diagnosis and a higher one year mortality.

10 **Young age:** SLE in children more severe,higher malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities

# Summary

## Systemic Lupus Erythematosus

Chronic, multisystem inflammatory disease characterized by autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.

### Etiology

- age (65% are between **15 - 65** years) & gender ( **F** >M)
- genetic ( **HLA-DR2, HLA-DR3** )
- **hormonal → estrogen (↑↑ in perimenopausal women)**
- racial (↑ in african americans)
- environmental (ultraviolet rays, silica dust, viruses, drug, etc..)

### Clinical features

1. Malar rash (butterfly rash)
2. Discoid rash
3. Photosensitivity (unusual reaction to sunlight)
4. Oral ulcer (pain **less** )
5. **Arthritis** (it is often the first symptom that brings the patient)
6. Serositis (pleuritis or pericarditis)
7. Renal disorder (persistent proteinuria or cellular casts)
8. Neurological disorder (seizures or psychosis)
9. Hematological disorder (hemolytic anemia or leukopenia or thrombocytopenia)
10. Immunological disorder ( **Anti-DNA** or Anti-Sm Ab or Antiphospholipid Ab)
11. **Antinuclear antibodies** ( **ANA** ) → most important marker!

Other symptoms: fever, fatigue, alopecia, weight loss, lymphadenopathy, GI symptoms, etc.

### Investigations

- Serology:
- **ANA** (elevated in almost all SLE pts) → sensitive but not specific
- **Anti-dsDNA** (40%) & **anti-Sm Ab** (30%) → very specific (presence is diagnostic!) but not sensitive
- Anti-SSA & Anti-SSB
- Antihistone Antibodies → in drug induced lupus (100%)
- Blood count: Normochromic, normocytic anaemia
- ESR: raised CRP: usually normal
- Urea and creatinine: rise when renal disease is advanced.
- Low serum albumin/high urine protein/creatinine ratio
- Histology: Characteristic deposition of IgG and complement in kidney or skin biopsies.

### Management

- Mild to moderate disease (restricted to skin and joints) → **NSAIDs** & hydroxychloroquine +/- steroids.
- Life threatening disease (renal, CNS, cardiac involvement) → High-dose corticosteroids and immunosuppressants (AZA, cyclophosphamide, rituximab)
- Maintenance → hydroxychloroquine is first line for long term disease control & glucocorticoids are best initial therapy in acute flares

### Prognosis

Poor prognostic factors for survival in SLE include :

- Renal disease (especially diffuse proliferative glomerulonephritis).
- Hypertension
- Renal and central nervous system (CNS) disease
- Young age (SLE in children more severe)

# Lecture Quiz

**Q1: A 33-year old woman presents to her primary care physician with bilateral joint pain. She says that the pain has been slowly worsening over the past 3 days. Otherwise she complains of fatigue , subjective fever and a sunburn on her face which she attribute to gardening, She is not aware of any chronic medical conditions and takes multivitamin daily , her temperature is 37.1 ,BP (125/64),pulse is 80, Respiratory rate 13/min, O2 sat 98% on room air. physical exam reveals bilateral redness over the maxillary prominence. Which of the following is the most likely to be seen in this patient?**

A. Decreased anti-dsDNA antibodies
B. Decreased complement levels
C. Increased anti-centromere antibodies
D. Increased anti-topoisomerase antibodies

**Q2: Which of the following genes are linked to SLE?**

A. HLA-B27
B. HLA-DR4
C. HLA-DR2
D. HLA-B51

**Q3: A 25-year-old female gives birth to a baby with complete heart block who subsequently requires pacemaker insertion. Which of the following antibodies is most likely to be detected in the maternal serum?**

A. Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies
B. Anti-endomysial antibodies
C. Anti-Ro/SSA antibodies
D. Anti-SCL70 antibodies

**Q4: A 34-year-old Afro-Carribean woman has been admitted for management and investigation of increasing shortness of breath. On further questioning, she mentions that her hands have been painful and stiff over the past few months and she has been having recurrent mouth ulcers. Chest x-ray confirms bilateral pleural effusions and blood tests reveal a raised ESR and a normal CRP. A diagnosis of systemic lupus erythematosus (SLE) is suspected and a full autoantibody screen is sent to the laboratory. Which of the following auto-antibodies is most specific to the suspected diagnosis?**

A. Anti-nuclear antibody
B. Rheumatoid factor
C. Anti-double stranded DNA antibody
D. Anti-centromere antibody
E. Anti-mitochondrial antibody

**Q5: A 47-year-old woman patient presents with a facial, macular 'butterfly rash'. Rheumatological investigations do not reveal that the patient has SLE. You suspect drug-induced SLE-like syndrome and assess her medication history. Which one of the following drugs is most likely to be responsible for this condition?**

A. Trimethoprim
B. Aspirin
C. Atenolol
D. Diclofenac
E. Lansoprazole

Answers: Q1:B | Q2:C | Q3:C | Q4:C | Q5:A

Answers Explanation File!

# GOOD LUCK !

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