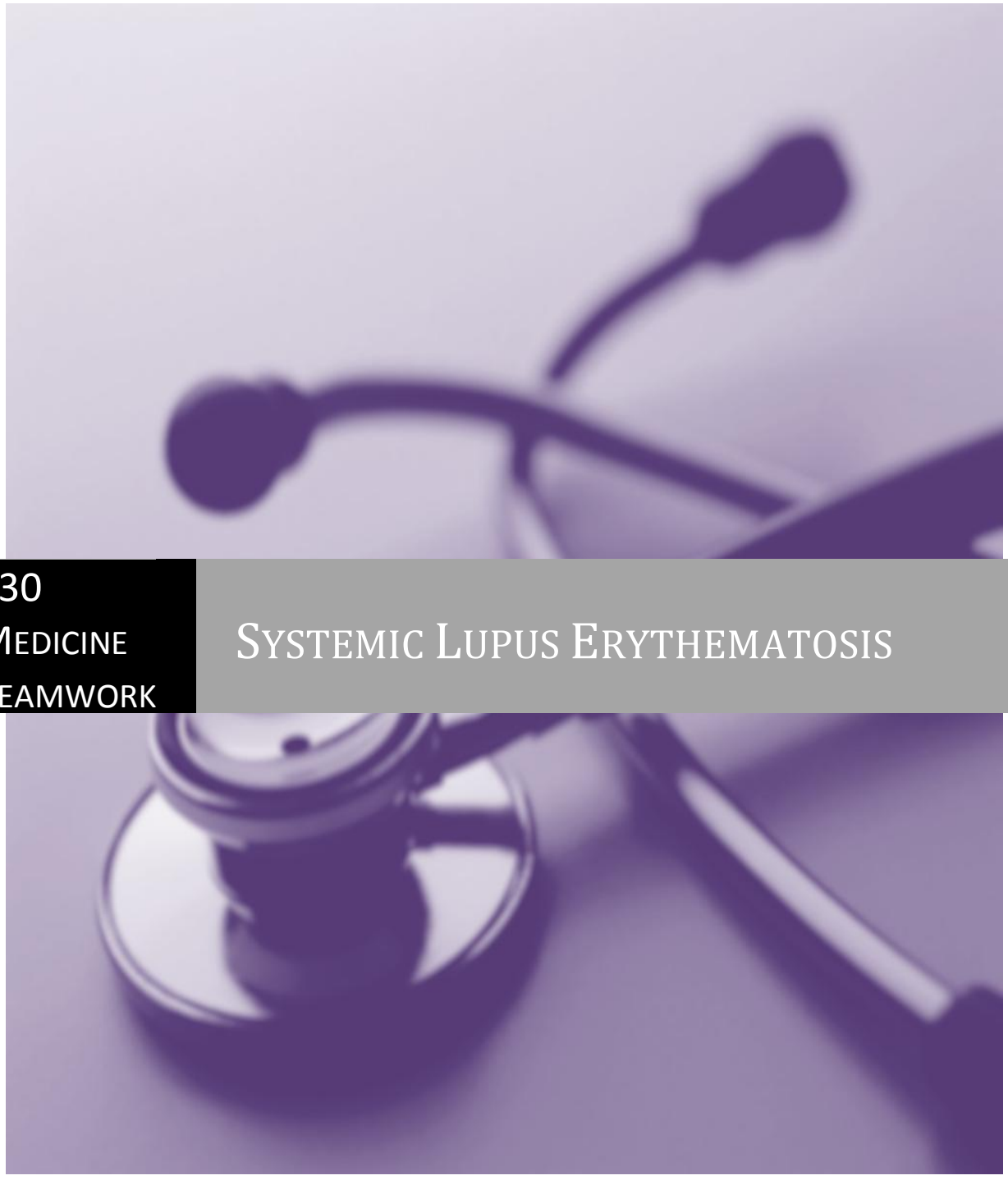
"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler



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MEDICINE
TEAMWORK

# SYSTEMIC LUPUS ERYTHEMATOSIS

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# Systemic Lupus Erythematosis

**Definition:**

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

**The eleven criteria to diagnose SLE:**

**1. Malar rash:**

Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.

**2. Discoid rash:**

Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.

**3. Photosensitivity:**

Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.

4. **Oral ulcers:**

It is usually painless, observed by physician.

**5. Arthritis:**

Involving two or more peripheral joints, characterized by tenderness, **swelling** or effusion.

**6. Serositis:**

a) Pleurtits: Pleuritic pain or rubbing heard by a physician or evidence of pleural effusion.
b) Pericarditis: Documented by ECG or rubbing heard by a physician or evidence of pleural effusion.

**7. Renal disorders: (The most common and most serious)**

a) Persistent proteinuria > 0.5 gm per day or > 3 gm if quantitation not performed.
b) Cellular casts: Red cells, hemoglobin, granular, tubular or mixed.

**8. Neurologic disorders:**

Seizures, or psychosis in the absence of offending drugs or known metabolic derangements. Eg. Uremia, ketoacidosis, or electrolyte imbalance.

**9. Hemolytic disorders:**

Any of the following disorders:

a) Hemolytic anemia with reticulcytosis.
b) Leukopenia < 4,000/mm <>3<> total on 2 or more occasions.
c) Lymphopenia < 1,500/mm <>3<> total on 2 or more occasions.
d) Thrombocytopenia < 100,00/mm <>3<> in the absence of offending drugs.

**10. Immunologic disorders:**

Any of the following disorders:

a) Positive finding of antiphospholipid antibodies: (Recently we are adopting this tests) based on:
   1. An abnormal serum level of IgG or IgM anticardiolipin antibodies.
   2. A positive test result for lupus anticoagulant using a standard method
   3. 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.
b) Anti-DNA.
c) Anti-Sm: antibody to Sm nuclear antigen.
d) False positive selelogic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.

**11. Antinuclear antibody:**

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.

## Epidemiology:

**Locally**: 2 cases of SLE among 10,372 studied (prevalence of 19.28 per 100,000).
**Internationally:** Denmark(21.7/100,000), Britain(12/100,000), India(3.2/100,000), Sweden(39/100,000).

## Etiology:

**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. (Male is less because of hormonal affect)
- 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, and other early components) are associated with an increased risk of SLE.

**Hormonal factors:**

1. F: M ratio of prevalence in different age groups:
   - In children, f:m ratio is 3:1.
   - In adults, f:m ratio is 10-15:1
   - In older, the ratio is approximately 8:1.
2. Age at onset:
   - 65% have onset between 16 and 55.
   - 20% before age 16.
   - 15%t after age 55.
3. Higher prevalence in men with Klinefelter disease. (Because they have an extra X chromosome)
4. Exogenous estrogen and exacerbations of SLE.
5. Men at all ages have the same risk of disease as women who are prepubertal or postmenopausal.
6. Males do not have an age-related peak in incidence.

**Racial and geography:**

- Higher prevalence (2.5- to 6-fold) in USA African American women than in white women. But, of course infrequently in Blacks in Africa.
- Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians.
- More common in urban than rural areas.
- Also 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.

**Environmental:**

- Worldwide variability of prevalence the disease. (Black in Africa and US)
- Influence of environmental factors on the course of the disease, e.g.:
  a. Ultraviolet light.
  b. Viruses.
  c. Drugs cause or exacerbate.
  d. Silica dust. (Like cosmetic surgeries)
  e. Cigarette smoking.
  f. Alfa Alfa sprouts.

## Pathophysiology:

Disturbances in the immune system:

- High ratio of CD4+ to CD8+ T cells.
- Defects in immune cell tolerance leading to production of autoantibodies targeting antigens located in nuclei, cytoplasm, on cell surfaces, and in plasma proteins.

- Autoantibodies lead to mostly immune complex formation (e.g. kidney) and direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).
- Cell-mediated autoimmunity also plays part.
- Tissue damage follows.

**Organ involvement in SLE:** **(Foreign study results)**

- Joints 90%
- Skin
  - Rashes 70%
  - Discoid lesions 30%
  - Alopecia 40%
- Pleuropericardium 60%
- Kidney 50%
- Raynaud's 20%
- Mucous membranes 15%
- CNS (psychosis/convulsions) 15%

**SLE – Presenting and Prevalent Symptoms:** **In Saudi Arabia**

- **Malar rash 47.9%**
- Discoid rash 17.6%
- **Photo sensitivity 30.6%**
- Oral ulcer 39.1%
- **Arthritis 73.9%**
- Serositis 27.4%
- Renal disorder 47.9%
- Neurological disorder 27.6%
- Hematological disorder 85.9%
- Immunological disorder 80.9%
- **ANA 99.7%**

**Other presenting symptoms**

- Splenomegaly 2.6%
- Hepatosplenomegaly 6.1%
- Genital ulcers 1.4%
- HTN 28.4%
- Myalogia 6.6%
- Pancytopenia 12.2%
- Pleuritis 15.8%
- Pericarditis 20.7%
- Pulmonary symptoms 28.0%
- Gastrointestinal symptoms 38.6%
- **Fever 30.6%**
- Weight loss 23.1%
- Fatigue 42.5%
- Arthralgia 86.9%
- Raynaud's phenomenon 8.7%
- Alopecia 47.6%
- Lymphadenopathy 20.0%
- DVT 7.4%
- Ascites 8.9%
- Hepatomegaly 3.2%

**Neurologic Signs or Symptoms:**

- Meninges: **Headache** and Meningismus.
- Cerebellum: Ataxia.
- Spine: Paraparesis and multiple sclerosis-like disorders.
- Cerebrum: Dementia, strokes, subarachnoid hemorrhages, migraines, other headaches.
- Cranial and peripheral sensory, motor neuropathies: Mononeuritis multiplex, myasthenia gravis, seizures, Guillain-Barre syndrome, Chorea, rigidity, tremor, SIADH.
  (Psychiatric manifestations are common.)

## Special considerations:

- **Drug-induced lupus:** (consider before diagnosing native lupus)
  - Sex ratios are nearly equal.
  - Nephritis and CNS not common. (Not as serious as native SLE)
  - No anti-native DNA or hypocomplementemia.
  - Resolution on discontinuation of drug.

## Drugs associated with lupus erythematosus:

- **Definite association**
  - Procainamide.
  - **Isoniazid.**
  - Quinidine.
  - Chlorpromazine.
  - **Methyldopa.**
  - Hydralazine.
- **Possible Association**
  - Ethosuximide.
  - Propylthiouracil.
  - Hydrazines.
  - Sulfasalazine.
  - Levodopa.
  - Sulfonamides.
  - Lithium.
  - Trimethadione.
  - Betablockers.
  - Methimazole.
  - Captopril.
  - Nitrofurantoin.
  - Carbamazepine.
  - Penicillamine.
  - Cimetidine.
  - Phenytoin.
- **Unlikely Association:**
  - Griseofulvin.
  - Streptomycin.
  - Methysergide.
  - Tetracyclines.
  - Oral contraceptive.
  - Allopurinol.
  - Penicillin.
  - Chlorthalidone.
  - Phenylbutazone.
  - Gold salts.
  - Reserpine.

## Treatment:

**General considerations:**

- Prevention: (You can't prevent the disease but you can prevent symptoms)
  - Avoid UV light and sun. (Sunsceening)
  - Antimalarial to prevent relapses.
  - Treat hypertension and dyslipidemias.
- Treat depending on the organ system(s) involved:
  - Skin, musculoskeletal, and serositis: NSAIDs, HCC, and local corticosteroids.
  - More serious organ involvement. (CNS, renal)
- Immunosuppression with high-dose steroids, AZA and/or cyclophosphamide, mycophenolate, and Tacrolimus.
- Targeted therapy (biological): rituximab.
- Other treatments
  - Plasma exchange for TTP or diffuse alveolar hemorrhage
  - Intravenous immunoglobulin for severe steroid-nonresponsive thrombocytopenia.

## Prognosis:

- **Poor prognostic factors for survival in SLE include:**
  - Renal disease. (especially diffuse proliferative glomerulonephritis)
  - Hypertension.
  - Renal and central nervous system disease.
  - Less education because of poor compliance.

  - Poor socioeconomic status because of inadequate access to medical care.
  - Black race because of their low socioeconomic status.
  - Presence of antiphospholipid antibodies.
  - High overall disease activity.
- **Male sex**
  - Men similar frequency of renal, skin, arthritis, and CNS as women.
  - Less photosensitivity.
  - More serositis.
  - An older age at diagnosis.
  - A higher one-year mortality.
- **Young age**
  - SLE in children more severe, higher malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities. (Why more sever? It is because the longer you live the more damage you get with the disease)

**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.

# Scleroderma

## Classification of scleroderma:

**1. Localized:**
Sub-classifications:
Morphea, plaque like, guttate, and generalized linear scleroderma.

**2. Generalized:**
With diffuse visceral involvement.
CREST syndrome. (Calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasia)
Overlaps with other connective tissue disease.

**3. Chemical-induced scleroderma-like conditions:**
E.g.: Vinyl chloride disease

**4. Diseases with skin changes mimicking scleroderma:**
E.g.: Scleredema

**5. Eosinophilic fasciitis:**

## Progressive Systemic Sclerosis: Preliminary Diagnostic Criteria

Patient must have major criterion or 2 minor criteria.

- **Major criterion:**
  Proximal scleroderma
- **Minor criterion:**
  Sclerodactyly
  Digital pitting or scars or loss of substance from finger pads
  Bibasilar paulmonary fibrosis

## Systemic manifestations of sclero-derma

**Pulmonary:** Dyspnea, cough, hemoptysis, pleuritic pain, and clubbing of nails.
**Gastrointestinal:** Dysphagia, dyspepsia, constipation, diarrhea, and malabsorption.
**Renal:** Proteinuria, azotemia, hypertension, and renal failure.
**Musculoskeletal:** Polyarthralgia, swelling of joints, and contractures.
**Cardiovascular:** Arrhythmias myocardial failure.

## Secondary Raynaud's phenomenon: classifications and causes:

**Connective tissue diseases:**
Systemic sclerosis, CREST.
SLE.
Mixed connective tissue disease
Rheumatoid arthritis
Dematomyositis/ polymyositis.
**Miscellaneius:**
Reflex sympathetic dystrophy.
Hypothyroidism.
Pheochromocytoma.
Neoplasm.
Primary pulmonary hypertension.
Variant angina.

# Mixed Connective Tissue Disease

## Clinical and laboratory features of MCTD:

- Polyarthritis.
- Raynaud's phenomenon.
- Swollen hands or sclerodactyly.
- Abnormal esophageal motility.
- Myositis.
- Low incidence of lupus nephritis.
- Hyperglobulinemia.
- Positive ANA (often speckled pattern)
- Antibody to nRNP.

| Positive Criterion | Algorithm of | |
|---|---|---|
| | Alarcon-Segovia and Villareal | Kahn and Appelboom |
| Serological test | Anti-(U1-RNP) titer ≥ 1:1600 | Anti-(U1-RNP) titer ≥ 1:1200 in a patient with an ANA titer ≥ 1:2560 and a speckled ANA pattern |
| Clinical features | ≥3; one of which must be synovitis or myositis, with others | ≥3; one of which must be Raynaud's phenomenon, with others |
| | To include:<br>• Swollen hands<br>• Raynaud's phenomenon<br>• Acrosclerosis | To include:<br>• Swollen fingers<br>• Synovitis<br>• Myositis |

## Antibodies Associated with Rheumatic Diseases: Percentages of Patients Affected

- Antibodies to native DNA➔ SLE 50% - 60% of patients.
- Anti-Sm antigen ➔SLE: 30% patients.
- Antibodies to histones ➔Drug-induced SLE: 95%, SLE: ≤ 60%, Rheumatoid arthritis: 20% patients.
- Antibodies to SS-A ➔Sjogren's syndrome: 70%, SLE: 30% - 40%, scleroderma and mixed connective tissue disease: frequency and titers low.
- Antibodies to SS-B ➔Sjogren's syndrome: 60%, SLE: 15% patients.
- Antibodies to RNP➔ Mixed connective tissue disease: 95% - 100%, SLE: 30% at low titers, scleroderma: 10% - 20%
- Antibodies to Scl-70 ➔ scleroderma: 10% - 20%
- Antibodies to nucleolar antigens➔ Scleroderma: 40% - 50%
- Antibodies to centromere antigens➔ CREST: 80% - 90%
- Antibodies to PM-1➔ Polymyositis: 50%, Dermatomyositis: 10%