

Systemic Lupus Erythematosus

Summary

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects women of childbearing age and is the most common form of lupus. The exact cause is still unknown, but hormonal and immunological features and genetic predisposition are considered likely etiological factors. Disease presentation is variable but is usually characterized by phases of remission and relapse. Symptoms can range from mild and localized 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. Involvement of the kidneys is common and can lead to lupus nephritis. Potential manifestations of SLE include cutaneous lupus erythematosus (CLE) and neuropsychiatric systemic lupus erythematosus (NPSLE); however, they can also occur independently from SLE. Other forms of lupus in addition to SLE include drug-induced lupus erythematosus (DILE) and neonatal lupus. The diagnosis of lupus is based on clinical findings and is further supported by laboratory studies, including the presence of antinuclear antibodies (ANAs) and antigen-specific ANAs (i.e., anti-dsDNA, anti-Sm). The 2019 EULAR/ACR classification criteria for SLE do not need to be fulfilled to make a diagnosis but may further support it. Management consists of general measures, such as avoiding sun exposure, and lifestyle modifications for ASCVD prevention. Long-term immunosuppressive therapy depends on disease severity and organ involvement; hydroxychloroquine is typically used, as it has been shown to reduce flares and decrease mortality. In severe cases, additional immunosuppressants (e.g., mycophenolate, azathioprine) or biological agents may be given. Cardiovascular, neurological, and renal disease (lupus nephritis), together with infections, are the main causes of death in patients with SLE.

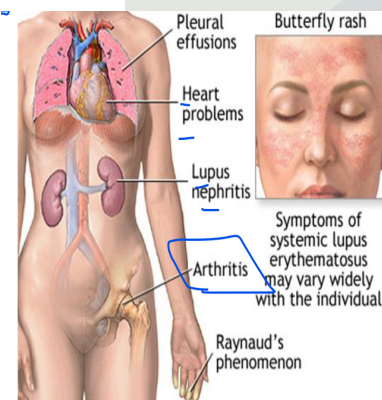
A. Definition. This multisystem autoimmune disorder is characterized by widespread chronic inflammation and immune complex-mediated vasculitis.

B. Epidemiology

1. There is a female predominance (female-to-male ratio is 8:1).
2. Age of onset is rarely younger than 10 years and peaks in adolescence.
3. SLE occurs most often in patients of Asian, African, or Latino ethnicity.

ETIOLOGY

- SLE is a multisystem disorder of unknown etiology characterized by the production of large amounts of circulating autoantibodies.
- This antibody production due to loss of T lymphocyte control on B lymphocyte activity, leading to hyperactivity of B lymphocytes, which leads to nonspecific and specific antibody and autoantibody production.
- These antibodies form immune complexes, which can get trapped in the microvasculature, leading to inflammation and ischemia.
- Autoantibodies (ANA, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, antiphospholipid antibody: in descending order of prevalence) may precede the onset of SLE by 9 yr, suggesting a presymptomatic state of autoimmunity.
- HLA types (HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency among patients with lupus.



Pathophysiology

The exact pathomechanism of SLE is not fully understood, but the following two processes are the most widely accepted hypotheses: [5]

- **Autoantibody development:** deficiency of classical complement proteins (C1q, C4, C2) → failure of macrophages to phagocytose immune complexes and apoptotic cell material (i.e., plasma and nuclear antigens) → dysregulated, intolerant lymphocytes targeting normally hidden intracellular antigens → autoantibody production (e.g., ANA, anti-dsDNA)
- **Autoimmune reactions**
 - Type III hypersensitivity (most common in SLE) → antibody-antigen complex formation in microvasculature → complement activation and inflammation → damage to skin, kidneys, joints, small vessels
 - Type II hypersensitivity → IgG and IgM antibodies directed against antigens on cells (e.g., red blood cells) → cytopenia

Clinical Finding:

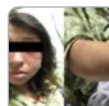
Skin disease findings:

1. **MALAR "BUTTERFLY" RASH:** common raised, erythematous rash on the cheeks, across the bridge of the nose, on the forehead, and chin, but spars the nasolabial folds. 33% of pediatric SLE onset. No scarring. Precipitated by sun- exposure.
2. **PHOTOSENSITIVITY:** problematic during the summer months
3. **DISCOID LUPUS,** is an inflammatory process that leads to disruption of the dermal-epidermal junction, cause scarring and loss of pigmentation in the affected area. If occurs in the scalp, alopecia ensues. Only 2-3% of all DLE occurs in childhood.



4. **RAYNAUD PHENOMENON,** not specific for SLE
5. **LIVIDO RETICULARIS,**
6. **OTHERS:** erythematous macular eruptions (particularly on fingers, palms, and soles), purpura, sub-acute psoriasiform or annular skin lesions, bullous or urticarial lesions, and alopecia.

- **MOUTH AND NASAL SORES** resulting from mucosal ulceration are a common complaint in patients with SLE. can lead to ulceration and perforation of the nasal septum.
- **LYMPHADENOPATHY AND SPLENOMEGALY** are common findings in SLE. Because of reticuloendothelial system stimulation (axillary lymphadenopathy can be a sensitive indicator of disease activity)
- **SEROSITIS** with chest pain and pleural or pericardial friction rubs or frank effusion.
- **RENAL INVOLVEMENT** is one of the most serious manifestations of SLE and is common in pediatric SLE,
 - ✓ occurring in 50% to 70% of children.
 - ✓ range from microscopic proteinuria or hematuria to gross hematuria, nephrotic syndrome, and renal failure.
 - ✓ Hypertension or the presence of edema should clue to the risk of lupus renal disease.
- **ARTHRALGIAS AND ARTHRITIS** is rarely deforming and typically involves the small joints of the hands, although any joint may be involved.
- **MYALGIAS OR FRANK MYOSITIS,** with muscle weakness and muscle fatigability.
- **CNS,** leading to symptoms ranging from symptoms, such as poor school performance and difficulty concentrating, to seizures, psychosis, and stroke.
- The occurrence of arterial or venous thrombosis suggesting antiphospholipid antibody syndrome, associated with :
 - ✓ recurrent fetal loss
 - ✓ livedo reticularis
 - ✓ thrombo-cytopenia
 - ✓ Raynaud phenomenon



Presenting Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, prolonged fever, lymphadenopathy
Musculoskeletal	Arthralgias, arthritis
Skin	Malar rash, discoid lesions, livedo reticularis, vasculitis
Renal	Glomerulonephritis, hypertension, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis (cardiac tamponade). valvular thickening and verrucous endocarditis (Libman-Sacks disease).
Neurologic	Seizures, psychosis, stroke, cerebral venous thrombosis, pseudotumor cerebri, aseptic meningitis, chorea, global cognitive deficits, mood disorders, transverse myelitis, peripheral neuritis (mononeuritis multiplex)
Pulmonary	Pleuritic pain, pulmonary hemorrhage, Pneumonitis
Hematologic	Coombs-positive hemolytic anemia, anemia of chronic disease, thrombocytopenia, leukopenia
Gastrointestinal	Pancreatitis, Mesenteric, arteritism Serositis, Hepatomegaly, Hepatitis (chronic lupoid), Splenomegaly
Reproduction	Repeat spontaneous abortions, Neonatal lupus erythematosus, Congenital heart block
Laboratory	Elevated ESR and CRP; decreased C3 or C4; positive ANA and anti-double-stranded DNA antibodies

F. Laboratory findings

1. **Elevated ESR**
2. **Anemia** (anemia of chronic disease or hemolytic anemia)
3. **Leukopenia**
4. **Thrombocytopenia**
5. Urinalysis may show **proteinuria** depending on the extent of renal disease.
6. **Rheumatologic markers**
 - a. **ANA** is almost **universally elevated** (>99%) in SLE and is an **excellent screening test**. However, ANA is **nonspecific** for SLE and is found in many other diseases.
 - b. **RF** is often elevated in SLE, but like ANA, is **nonspecific**.
 - c. **Anti-double-stranded DNA (anti-dsDNA) antibodies** are much more **specific** (found only in SLE), and their **levels can be used as markers for active disease**, especially nephritis.
 - d. **Anti-Smith (anti-Sm) antibodies** are less prevalent in patients with SLE but, when present, are **very specific**. Unlike anti-dsDNA, anti-Sm antibody levels cannot be used as a measure of disease activity.

7. Other findings

- a. **Antiphospholipid antibodies** (e.g., positive lupus anticoagulant or anticardiolipin antibodies) present in patients with SLE **reflect an increased risk of thrombotic events**.
- b. **Decreased complement (C3 and C4)** is seen especially with active disease and represents immune complex-mediated complement activation.
- c. **Ro (SSA) and La (SSB) antibodies** are less strongly associated with SLE (**more specific for Sjögren syndrome**). Babies born to mothers with these antibodies are at risk for neonatal lupus.

• DRUG-INDUCED LUPUS:

- ✓ is a lupus-like disease that is precipitated by exposure to certain drugs (**anticonvulsants, sulfonamides, and antiarrhythmic agents**)
- ✓ The finding of antihistone antibodies suggests antigenic similarities between these drugs and histone proteins leading to cross-reactive immune reactions.
- ✓ The typical symptoms: fever, rash, and pleuropericardial disease typically abate with discontinuation of the drug.
- ✓ The serum complement usually remains normal
- ✓ complications, including renal disease, are rare



TREATMENT

- **Corticosteroids** are the **mainstay of treatment** for SLE..
 - ✓ systemic disease are **often started on 1-2 mg/kg/24 hr of oral prednisone** in divided daily doses.
 - ✓ When complement levels **increase to within the normal range**, the dose is **carefully tapered to the lowest effective dose**.
- **NSAIDs** have been used to **treat the arthralgias and arthritis** associated with SLE. are used with caution because **patients with lupus are more susceptible to hepatotoxicity**.
- **Hydroxychloroquine** is used for:
 - ✓ **treatment of lupus skin disease, such as discoid lupus**
 - ✓ **reduce the risk of thromboembolic disease and lowers lipid levels**.
 - ✓ **maintenance therapy**
 - ✓ **longer periods of wellness between flares of disease**
 - ✓ **decreased numbers of flares**.
- For **lupus nephritis or cerebritis**, **Cyclophosphamide[®]** is used. It shows **significant decreased rates of progression to renal failure**.
- For patients who are **not able to tolerate the tapering of their corticosteroids**, the use of **steroid-sparing agents**, such as **azathioprine[®]** or **methotrexate** may be indicated.
- sun has been shown to lead to flares of the disease.
- Worse prognoses are seen in patients with severe lupus nephritis or cerebritis, with risk of chronic disability or progression to renal failure.
- patients benefit from supplementation with **calcium and vitamin D** to reduce the risk of **osteoporosis that may result from prolonged cortico-steroid use**.
- Patients with thrombosis and antiphospholipid antibodies or a lupus anticoagulant should receive **anticoagulant medication at least until lupus is in remission**. The length of therapy is controversial. **Low molecular weight heparin** is the anticoagulant of choice.
- renal biopsy for staging can help determine whether an immunosuppressive agent such as cyclophosphamide needs to be added to a corticosteroid regimen.
- ❖ **Class I**: minimal mesangial change without proteinuria or hematuria.
- ❖ **Class II**: mesangial proliferation.

EXCELLENT
PROGNOSIS

- ❖ **Class III (focal proliferative glomerulonephritis)** shows involvement of **<50% of glomeruli having focal, segmental proliferation of cells near capillaries with necrosis and lymphocytic infiltration**, and is often **associated with chronic renal disease**.
- ❖ **Class IV (diffuse segmental or global proliferative glomerulonephritis)** exhibits a **majority of each glomeruli affected by cellular infiltration, mesangial cellular proliferation, and crescent formation corresponding to scarring**, with **increased risk for developing end-stage renal disease in adulthood**; **intravenous pulse cyclophosphamide** can decrease this risk.
- ❖ **Class V disease (membranous glomerulonephritis)** shows **thickened capillary walls on light microscopy and subepithelial deposits on electron microscopy along the basement membrane**. associated with proteinuria
- ❖ **Class VI** is advanced sclerosing nephritis and demonstrates **diffuse, chronic damage suggesting progression to renal failure**.

COMPLICATIONS AND PROGNOSIS:

- the 5-yr survival rate is **>90%**.
- **Long-term complications** include **avascular necrosis** owing to corticosteroid use, infections, and myocardial infarction.
- **accelerated atherosclerosis**, based not only on prolonged cortico-steroid use, but also on the disease.
- Secondary infections with opportunistic organisms are the leading cause of mortality.



NEONATAL LUPUS

- Lupus in newborns results from maternal transfer of IgG auto-antibodies, usually anti-Ro/SSA or anti-La/SSB, between the 12th and 16th wk of gestation.
- Only a small percentage of offspring of mothers with autoantibodies to Ro and/or La develop disease.
- Symptoms usually derive from a single organ, although multiple organ involvement may
 - ✓ congenital heart block
 - ✓ cutaneous lesions, occur after ultraviolet exposure at about 6 wk of life and last 3-4 mo, on the face and scalp, 25% of rashes scar.
 - ✓ Hepatitis
 - ✓ thrombocytopenia
 - ✓ neutropenia
 - ✓ pulmonary and neurologic disease.
- Treatment is supportive.
- CHB is permanent and often requires cardiac pacing, either after birth or antenatally.
- Even infants of asymptomatic mothers with lupus may have slightly prolonged PR intervals.
- Cardiomyopathy is a rare serious sequel.
- NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE: (D/D)
 - ✓ a rare syndrome characterized by fever, rash, arthropathy, chronic meningitis, seizures, uveitis, and lymphadenopathy.
 - ✓ resulting from defective IL-1 regulation in the innate immune system
 - ✓ Anakinra, an IL-1 antagonist, has been very successful in the treatment of a small cohort of these patients

