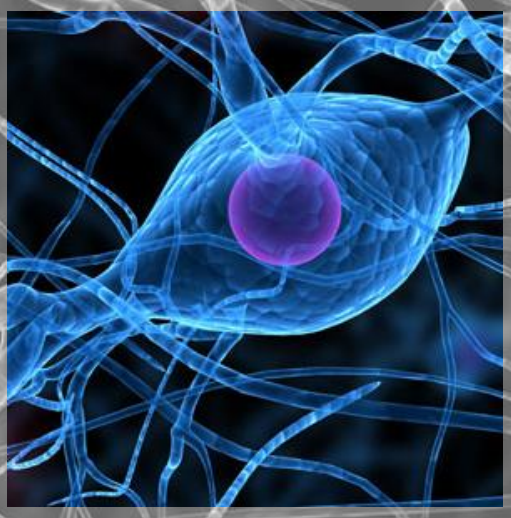
The Researcher's Ultimate Guide

Systemic Lupus Erythematosus



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Section 1:
Understanding Systemic Lupus Erythematosus

What is Systemic Lupus Erythematosus?

Systemic lupus erythematosus, commonly called SLE, is a chronic autoimmune disorder that causes protracted inflammation in almost any organ system, but most frequently affects the skin, joints, kidneys, blood cells, and nervous system. With this disease, the body fails to differentiate its own tissues from invading pathogens causing the immune system to launch an attack on the body's own healthy tissues. Of the four forms of lupus–SLE, discoid, neonatal, and drug-induced–SLE is the most common, accounting for approximately 70% of all lupus cases.

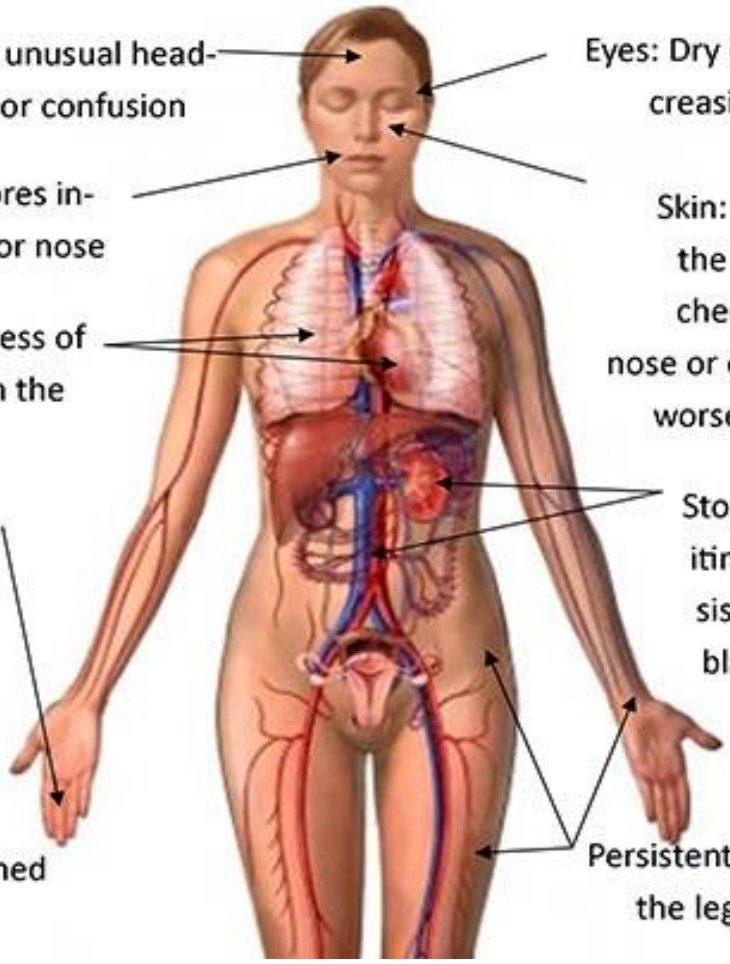
What are the symptoms of SLE?

SLE symptoms vary extensively from patient to patient. The severity and number of symptoms experienced generally increase with disease progression.

Primary Symptoms	Secondary Symptoms
• fatigue • fever • arthritic pain • malar ("butterfly") facial rash • flaky spots on upper body • sores/bumps on face & chest • swollen glands • light sensitivity • headaches • sudden chest pain	• weight loss • memory loss • bloody urine • numbness • anxiety/depression • swelling of extremities • anemia • complications in any organ

Common Lupus Symptoms

Symptoms of SLE may vary widely between individuals.



Source: http://www.mollysfund.org/learn-about-lupus/symptoms/

Symptoms of SLE can range from mild to severe:

Mild

Symptoms are easily recognized and treated. i.e. skin rash, headaches, fatigue, mild pain

Moderate

Abnormal white or red blood cell counts. Typically this classification is blended with the severe category since blood involvement almost always indicates future organ system involvement.

Severe

Disease affects major organs/organ systems.

Do SLE patients always exhibit symptoms?

No.SLE follows a relapsing and remitting course marked by symptomatic flare-ups and asymptomatic periods of quiescence. Ninety-four percent of lupus patients are actively treated, even if they are in an asymptomatic state.

Inactive Disease

"Periods of quiescence." Patient is still taking daily medication and does not exhibit symptoms.

Flare-ups

Patient is experiencing symptoms above their baseline symptoms. Typically, a lupus flare involves all previous symptoms plus new ones at each flare. Flare-ups generally occur between 3-6 times a year and can last anywhere from a few hours to several months and in some cases, even years. The occurrence of flare-ups is unpredictable and irregular.

Who is affected by SLE?

SLE is 9 times more prevalent in women than men and 2-3 times more prevalent in African American, Hispanic, Asian, and Native American populations than Caucasian. Symptoms of SLE frequently appear during the peak childbearing years between the ages of 15-35. Although children can be diagnosed with SLE, it is very rare in children under 5.

What causes SLE?

Both genetic and environmental factors are implicated in SLE development. Research shows that 8% of affected patients have at least one first-degree family member (parents, siblings, and children) with SLE. Over 35 genes are currently known to increase the risk of developing SLE.

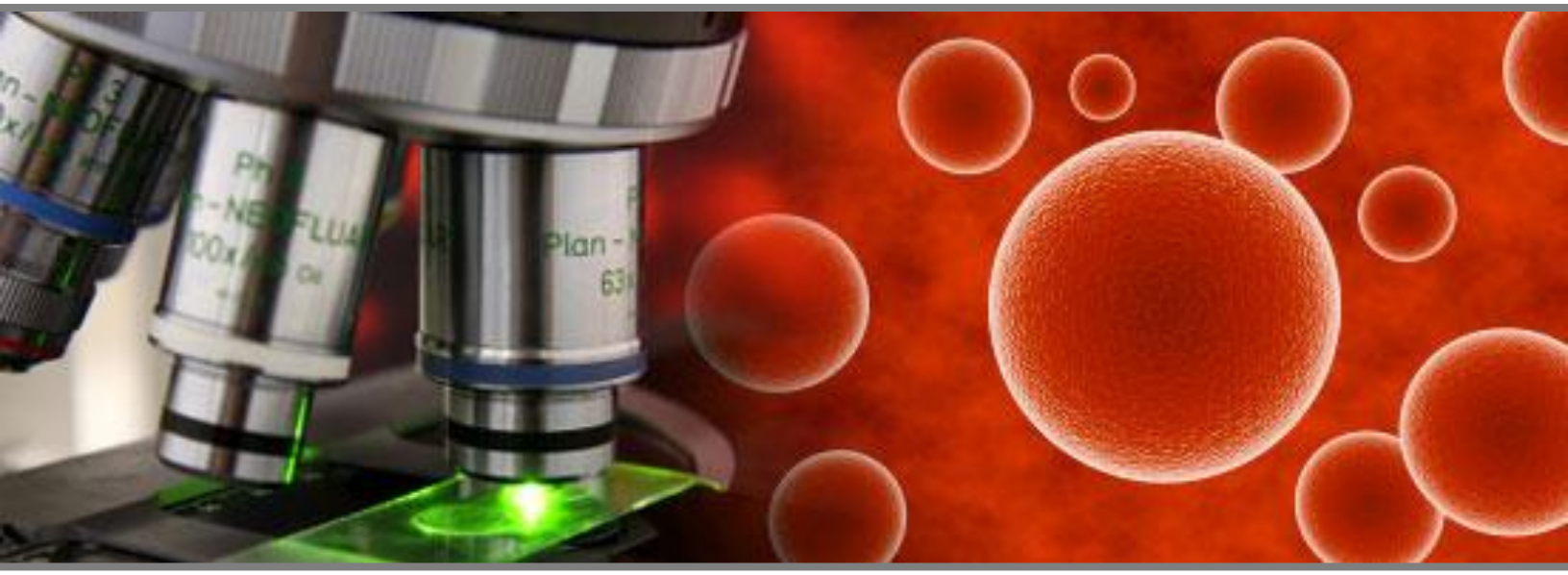
Environmental triggers and/or causes have been harder to identify. Some suspected factors associated with an increased risk of developing SLE include exposure to silica dust, smoking, ultraviolet light, and estrogen administration in postmenopausal women. Exposure to certain viruses and bacteria may also play a role. Several drugs, such as hydralazine and quinidine, work by stimulating the immune system and can cause drug-induced lupus. Drug-induced lupus enters remission upon discontinuation of these medications.

What is the prognosis for SLE patients?

With proper treatment, the current SLE survival rate is 95% at 5 years and 70% at 20 years in the United States.

Did You Know?

- The Lupus Foundation of America estimates that approximately 1.5 million Americans suffer from SLE.
- More than 16,000 Americans are diagnosed with lupus every year.
- SLE accounts for 70% of all lupus cases. Of those, approximately 50% are considered severe cases.
- An analysis of 2004 data from the Nationwide Inpatient Sample estimated the occurrence of 13,000 hospitalizations with a principal diagnosis of SLE and 141,000 hospitalizations with a principal or secondary diagnosis of lupus.
- Lupus was listed for 1,032,000 ambulatory care visits annually from 2001-2005.
- There were no new treatments for lupus in over 50 years until the 2011 FDA approval of belimumab.



Statistics obtained from http://www.cdc.gov/arthritis/basics/rheumatoid.htm

Section 2:
From the Real World to the Lab

How is SLE diagnosed?

Diagnosing SLE is especially difficult because it shares several symptoms with other autoimmune disorders such as fibromyalgia, scleroderma, rheumatoid arthritis, and chronic fatigue syndrome. Most patients live with the disease for over 2 years before a diagnosis is made. Ninety percent of SLE patients are diagnosed by a rheumatologist.

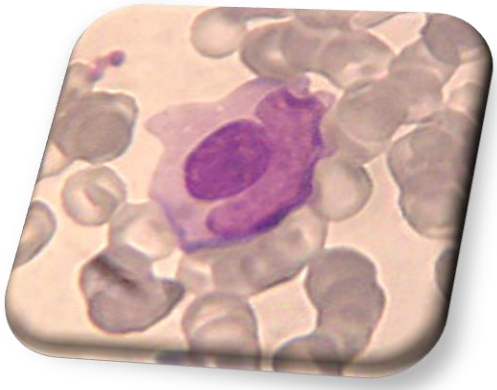
According to the American College of Rheumatology, SLE can be diagnosed if any 4 or more of the following 11 criteria are present, serially or simultaneously, during any interval of observation.

Criterion	Definition
Malar Rash	Fixed, flat, or raised erythema over the malar eminences, tending to spare the nasolabial folds
Discoid Rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging (older lesions may demonstrate atrophic scarring)
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history, or physician observation
Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving 2 peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	One or more of the following conditions: A) Pleuritis: Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion (B) Pericarditis: Documented by ECG or rub or evidence of pericardial effusion
Renal Disorder	One or more of the following conditions: (A) Persistent proteinuria >0.5 g/day or >3+ if quantization not performed (B) Cellular casts: May be red blood cell, hemoglobin, granular, tubular, or mixed

Criterion	Definition
Neurologic Disorder	One or more of the following conditions: (A) Seizures: In the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, electrolyte imbalance) (B) Psychosis: In the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, electrolyte imbalance)
Hematologic Disorder	One or more of the following conditions: (A) Hemolytic anemia with reticulocytosis (B) Leukopenia: < 4000/mm^3 total on 2 occasions (C) Lymphopenia: < 1500/mm^3 on 2 occasions (D) Thrombocytopenia: < 100,000/mm^3 in the absence of offending drugs
Immunologic Disorder	One or more of the following conditions: (A) Anti-DNA: Antibody to native DNA in abnormal titer (B) Anti-Sm: Presence of antibody to Smith (Sm) nuclear antigen (C) Positive finding of antiphospholipid antibodies 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, or (3) a false-positive serologic test for syphilis known to be positive for 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
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

What are LE cells?

LE cells are immune cells that have “taken in” dead cells. The dead genetic material is visible as an LE body. In the past, LE cell presence was used to diagnose SLE, but it is no longer used as diagnostic criteria because only 50-75% of SLE cases have LE cells.



LE Body

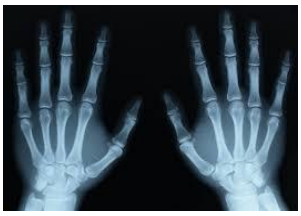
What tests are used in diagnosis?

The types of tests used in diagnosis vary extensively according to the symptoms presented in the suspected SLE patient. Not all tests, imaging studies, and procedures are performed on every patient.

Laboratory Tests

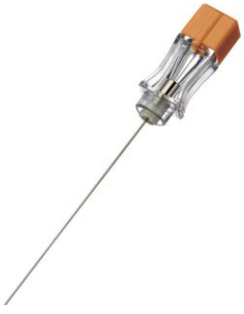
- **CBC with differential -** complete blood count, anemia indicates a flare-up
- **Creatinine and urea -** increased levels indicate lupus-related kidney damage
- **ESR -** Erythrocyte sedimentation rate tests for inflammation, high ESR correlates with a flare-up
- **ANA -** presence of anti-DNA antibodies, specifically anti-dsDNA and anti-Smith protein, indicates a flare-up
- **C3 and C4 -** low levels of these proteins indicate lupus-related inflammation
- **Lipids -** high levels indicate lupus-related heart disease
- **Bone density tests -** low bone density indicates lupus-related osteoporosis. Only rarely performed on lupus patients.

Imaging Tests



- **Joint radiography -** used to monitor lupus-related osteopenia and soft-tissue swelling
- **Chest radiography and chest CT -** used to monitor interstitial lung disease and to assess for pneumonitis, pulmonary emboli, and alveolar hemorrhage
- **Echocardiography -** used to assess for pericardial effusion, pulmonary hypertension, or verrucous Libman-Sacks endocarditis
- **Brain MRI/MRA -** used to evaluate for central nervous system (CNS) lupus white-matter changes , vasculitis, or stroke

Procedures



- **Arthrocentesis -** joint effusion fluids are straw-colored or clear in noninflammatory cases and either cloudy or yellow in inflammatory ones
- **Lumbar puncture -** may be performed to exclude infection with fever or neurologic symptoms
- **Renal biopsy -** used to confirm and improve treatment for lupus nephritis

Treating SLE

How is SLE treated?

Currently, there is no cure for SLE. Treatment involves both pharmacotherapy and lifestyle changes. To control potential flare-ups, most patients receive continuous treatment regardless of the active or inactive status of their SLE-related symptoms. Consequently, it is difficult to find patients not currently receiving treatment.

What are the most common drugs taken for SLE?

Plaquenil is most commonly prescribed antimalarial drug used to control SLE symptoms. Advil, Motrin, Celebrex, Aleve, prednisone, cyclophosphamide, methotrexate, Lovenox, and Coumadin are other common drug therapies.

Anti-inflammation

Primary

Drugs

NSAIDs:
- Ibuprofen (Motrin/Advil)
- Naproxen (Aleve/Naprosyn)
- Celecoxib (Celebrex)

Steroids:
- Prednisone
- Methylprednisolone (Medrol)

Others:
- Nabumetone (Relafen)
- Indomethacin (Indocin)

Dosages

NSAIDs:
- Usually low due to long-term usage
- "Low" varies depending on NSAID

Steroids:
High: 100-1,000 mg over a few days
Med.: 15-100mg over a few days
Low: 5-15 mg

Notes:
- Steroids are taken daily
- Doctors prefer to limit steroid prescription.

Side Effects

- bleeding ulcer
- abnormal kidney function
- stomach irritation
- blindness
- muscle weakness
- osteoporosis
- high blood pressure
- high glucose
- impaired blood clotting

Immuno-suppression

Secondary

Drugs

Cyclophoshamide (Cytoxan)	Methotrexate (Rheumatrex)	Azathioprine (Imuran)

Dosages

Standard:	**High**:	**Note:**
750mg/month over 6 months	50 mg/day over 4 days	The majority of patients maintain a standard regimen

Side Effects

- herpes zoster (shingles)
- increased risk for cancer
- increased risk for infection
- hormonal imbalance
- hair loss
- sterility
- bladder problems
- liver cirrhosis
- mouth sores
- headaches
- pancreatitis
- hepatitis
- nausea

Analgesia

Drugs

Range from acetaminophen (Tylenol) to narcotics

Dosages

Highly variable depending on drug

Side Effects

- liver function impairment
- addiction

Anti-malarials: Side Effect Reduction

Drugs

- Hydroxychloroquine (Plaquenil)
- Chloroquine (Aralen)

Dosages

High: 400 mg/day
Low: 200 mg/day
Patients are equally likely to be on either dosage at any given time

Side Effects

- upset stomach
- eye damage
- skin color change

Anti-Coagulants

Drugs

- Aspirin
- Heparin
- Warfarin (Coumadin)

Dosages

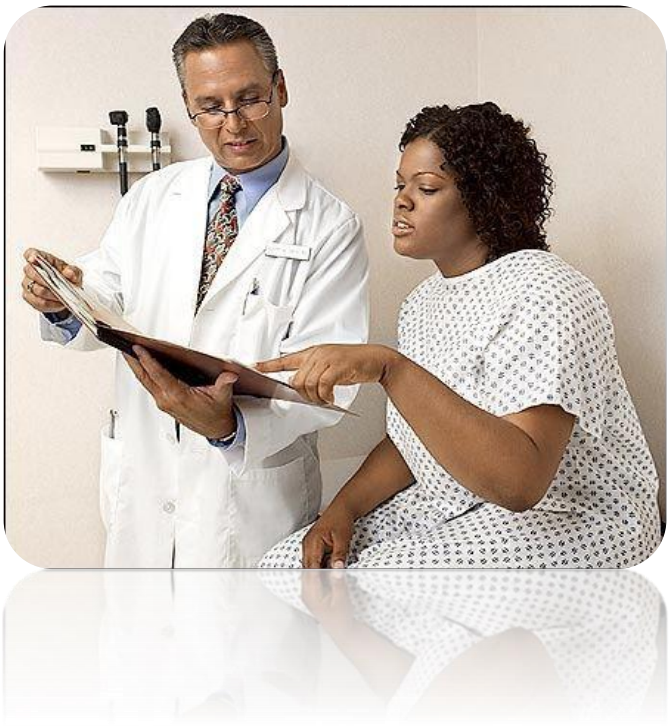
Aspirin: 70-80 mg/day
Heparin: 1-3 mg/day
Warfarin: highly variable

Side Effects

- overly thin blood
- excessive bleeding
- inability to clot properly

Patient Lifestyle

Doctor visits



SLE can become active at any time, for any duration, and at any degree of severity. Typically, each flare-up is worse (involves more symptoms) than the one before. No matter the degree of activity or inactivity, lupus patients usually attend regular doctor visits increasing in frequency as the disease progresses. A lupus status test is ***not*** done at each visit, but rather only when the patient's health has altered. SLE patients usually keep their disease under control through medications and do not require laboratory blood work at every doctor visit.

Lifestyle Changes

In addition to traditional drug treatment, an important component of controlling SLE is maintaining a healthy lifestyle . Patients are encouraged to pursue the following four lifestyle changes to optimize their treatment outcomes.

Important Lifestyle Changes

Stay Active

SLE patients should engage in light-to-moderate exercise interspersed with periods of rest. Exercise helps maintain joint flexibility, improve heart function, and reduce fatigue and depression.

Prevent Infections

SLE patients should stay up to date on their immunizations and should be careful to avoid individuals with communicable diseases. Hand washing and other careful hygiene practices, including dental hygiene, are important.

Avoid SLE Triggers

SLE triggers differ from person to person. In general, SLE patients should limit their exposure to sunlight and use hypoallergenic cosmetic products. Smoking and secondhand smoke exposure should be avoided.

Reduce Stress

SLE patients should get at least 8 hours of sleep at night. Naps during the day may be helpful in fighting bouts of fatigue. Maintaining social activities may also help prevent problems with depression and anxiety which are often associated with the disease.

Section 3:
Research Challenges

Physicians define an active course of SLE differently than do researchers. Physicians define active as "symptomatic"—is the patient experiencing symptoms of SLE or not? Researchers prefer to rely on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and/or British Isles Lupus Assessment Group (BILAG)—scales designed to assess and categorize the level of disease activity for diagnosis and observation. They are used by researchers in clinical trials, but rarely, if ever, by the physicians treating lupus patients. *Patients cannot be targeted based on these scores.*

SLEDAI

SLEDAI includes clinical tests (rashes, hair loss, etc.) and laboratory tests (blood tests, urinalysis, etc.) in the scoring index. Scores range from 0 to 105; a score greater than 20 is rare. *Physicians do not use this index to define disease activity*.

Scoring Index

Active Disease: ≥6

Mild/Moderate Flare:
Change >3 from previous score

Severe Flare:
Change >12 points from previous score

BILAG

BILAG is a score that attempts to assess a "need to treat" organ-by-organ. Scores range from A (very active) to E (not involved) and are broken into 8 organ groups. *Physicians do not use BILAG to assess their patient's level of disease activity. This test can be performed and provided with additional data, but it is not something that can be targeted*.

Scoring Index

A – very active
to
E – Not Involved

Targeting Capabilities

- Tissue removal is not a part of treatment for SLE patients, so tissue is not something that can be targeted from consented patients.
- Patients with active SLE can be targeted. SLEDAI/BILAG tests can be performed after collection to determine SLE activity level; however, patients cannot be targeted based on their score.
- Specimens available for collection from SLE patients include peripheral blood and blood derivatives (PMBCs, plasma, serum) and urine.

Section 4: Case Studies

Case 1: Pilot Study

Conversant Bio was asked to obtain several SLE samples for a well-established biotech company who needed samples to begin a pilot project. They asked that the samples be tested for HIV and HBV before being sent to their labs. Patients had to have active SLE and an anti-DNA antibodies test within the past 3 months. These samples were targeted, tested, and shipped within one week of Conversant receiving the purchase order.

Case 2: Timed to Meet Your Needs

A large pharmaceutical company asked Conversant Bio to find whole blood from 8 confirmed, active disease SLE patients and 8 patients with Sjögren's Syndrome for their project. The inclusion criteria required that patients not have been treated with biologics in the past 6 months. These samples were shipped in EDTA tubes according Conversant Bio's SOP. The researchers' specific request to receive samples on Mondays, Tuesdays, and Wednesdays with only one collection per day was successfully accommodated by Conversant Bio. This allowed the company to establish a more predictable and feasible project timeline.

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