Systemic Lupus Erythematosus

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Epidemiology

Prevalence: 20-240 per 100,000 persons

Incidence: 1-10 per 100,000 person-years

Higher prevalence in Asian, African-American, and Hispanic populations compared with white populations

Female predominance with a peak incidence during reproductive years
Epidemiology of systemic lupus erythematosus in Taiwan

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence rate per 10^5/year</th>
<th>Prevalence per 10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>F</strong></td>
<td><strong>M</strong></td>
</tr>
<tr>
<td>2000</td>
<td>17.6</td>
<td>2.3</td>
</tr>
<tr>
<td>2001</td>
<td>15.6</td>
<td>2.1</td>
</tr>
<tr>
<td>2002</td>
<td>14.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2003</td>
<td>14.3</td>
<td>1.7</td>
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<tr>
<td>2004</td>
<td>13.4</td>
<td>1.7</td>
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<tr>
<td>2005</td>
<td>12.8</td>
<td>1.9</td>
</tr>
<tr>
<td>2006</td>
<td>11.9</td>
<td>1.7</td>
</tr>
<tr>
<td>2007</td>
<td>11.9</td>
<td>1.7</td>
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Age specific incidence

F: Female, M: Male.
Pathogenesis
Contributors to systemic lupus erythematosus pathogenesis

In an individual who is genetically susceptible, plasmacytoid dendritic cells (pDCs) are activated by:

- Intracellular nucleic acids
- Debris derived from damaged or dying cells
- Exogenous triggers such as a virus

**Type I IFN** mediates numerous effects on immune system cells that mimic the response to a viral infection
The antigen-presenting capacity of myeloid dendritic cells can be augmented, promoting activation of self-reactive T cells and differentiation of B cells toward production of pathogenic antibodies.
Once autoantibodies are produced, **immune complexes** can:

- Amplify immune activation by accessing endosomal **Toll-like receptors (TLRs)** in pDCs and B cells
- Deposit directly in the vicinity of blood vessels, inducing complement activation, inflammation, and tissue damage
Endogenous stimuli for innate immune system activation

Self-DNA or self-RNA, either in association with HMGB1 or LL37 or in the form of immune complexes that bind Fc receptors, is internalized into endosomal Toll-like receptors (TLRs) and transducer signals that result in transcription of type I interferon and other proinflammatory cytokines.
Environmental triggers

Environmental factors that might play a role in the pathogenesis of systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</th>
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<tbody>
<tr>
<td>Ultraviolet B light</td>
<td>• Alfalfa sprouts and related sprouting foods containing canavanine</td>
</tr>
<tr>
<td>Probable</td>
<td>• Pristane and other hydrocarbons</td>
</tr>
<tr>
<td>Estrogen and prolactin</td>
<td>• Infectious agents other than EBV</td>
</tr>
<tr>
<td>EBV</td>
<td>• Bacterial DNA</td>
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<tr>
<td>Lupus-inducing medications</td>
<td>• Smoking</td>
</tr>
<tr>
<td>• Hydralazine</td>
<td>• Human retroviruses or endogenous retroelements</td>
</tr>
<tr>
<td>• Procainamide</td>
<td>• Endotoxins, bacterial lipopolysaccharides</td>
</tr>
<tr>
<td>• Isoniazid</td>
<td>• Vitamin D deficiency</td>
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<tr>
<td>• Hydantoins</td>
<td></td>
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<tr>
<td>• Chlorpromazine</td>
<td></td>
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<tr>
<td>• Metyldopa</td>
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<tr>
<td>• Penicillamine</td>
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<tr>
<td>• Minocycline</td>
<td></td>
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<tr>
<td>• Tumor necrosis factor inhibitors</td>
<td></td>
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<tr>
<td>• Interferon-α</td>
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</tbody>
</table>
Female predominance

- Hormone
- Chromosome
- Ovulation
Clinical features
## Criteria for the classification of SLE
- 1997 update of the 1982 revised ACR classification criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td><strong>Malar rash</strong></td>
<td>Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds</td>
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<tr>
<td><strong>Discoid rash</strong></td>
<td>Erythematous raised patches with adherent keratotic scale and follicular plugging; atrophic scarring may occur in older lesions</td>
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<tr>
<td><strong>Photosensitivity</strong></td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
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<tr>
<td><strong>Oral ulcers</strong></td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
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<tr>
<td><strong>Arthritis</strong></td>
<td>Nonerosive arthritis involving two or more peripheral joints</td>
</tr>
<tr>
<td><strong>Serositis</strong></td>
<td>a. Pleuritis—convincing history of pleuritic chest pain or rub heard by a physician or evidence of pleural effusions or b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion</td>
</tr>
<tr>
<td><strong>Renal disorder</strong></td>
<td>a. Persistent proteinuria &gt;0.5 g/day, &gt;3+ if quantification not performed or b. Cellular casts: may be red blood cell, hemoglobin, granular tubular, or mixed</td>
</tr>
<tr>
<td><strong>Neurologic disorder</strong></td>
<td>a. Seizures: in the absence of offending drugs or known metabolic derangements or b. Psychosis: in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td><strong>Hematologic disorder</strong></td>
<td>a. Hemolytic anemia with reticulocytosis or b. Leukopenia &lt;4000/mm³ or c. Lymphopenia &lt;1500/mm³ or d. Thrombocytopenia &lt;100,000/mm³ in the absence of offending drugs</td>
</tr>
<tr>
<td><strong>Immunologic disorder</strong></td>
<td>a. Anti-DNA: antibody to native DNA in abnormal titer or b. Anti-Smith: presence of antibody to Sm nuclear antigen or c. Positive finding of antiphospholipid antibodies</td>
</tr>
<tr>
<td><strong>Positive ANA</strong></td>
<td>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 syndromes</td>
</tr>
</tbody>
</table>
Frequencies of various manifestations of systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td><strong>Constitutional symptoms</strong> (fatigue, fever, weight loss)</td>
<td>90%-95%</td>
</tr>
<tr>
<td><strong>Mucocutaneous involvement</strong> (malar rash, alopecia, mucosal ulcers, discoid lesions, etc.)</td>
<td>80%-90%</td>
</tr>
<tr>
<td><strong>Musculoskeletal involvement</strong> (arthritis/arthralgia, avascular necrosis, myositis, etc.)</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Serositis (pleuritis, pericarditis, peritonitis)</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>40%-60%</td>
</tr>
<tr>
<td>Neuropsychiatric involvement (cognitive impairment, depression, psychosis, seizures, stroke, demyelinating syndromes, peripheral neuropathy, etc.)</td>
<td>40%-60%</td>
</tr>
<tr>
<td>Autoimmune cytopenia (anemia, thrombocytopenia)</td>
<td>20%-30%</td>
</tr>
</tbody>
</table>
• SLE tends to be more severe in men and in pediatric patients

Late-onset SLE (>50 y/o)
- More insidious onset
- More serositis and pulmonary involvement
- Less malar rash, photosensitivity, alopecia, Raynaud's phenomenon, neuropsychiatric disease, and nephritis
Cutaneous manifestations

• Lupus erythematosus **specific** skin lesions
  • Acute cutaneous LE (ACLE)
  • Subacute cutaneous LE (SCLE)
  • Chronic cutaneous LE (CCLE)

• Lupus erythematosus **non-specific** skin lesions
  • Cutaneous vascular disease, nonscarring alopecia, sclerodactyly, rheumatoid nodules, calcinosis cutis, LE-nonspecific bullous lesions, urticarial, papulonodular mucinosis, cutis laxa/anetoderma, acanthosis nigricans, erythema multiforme (Rowell’s syndrome), leg ulcers, lichen planus
Butterfly rash or malar erythema

Characterized by confluent, macular or papular erythema lasting days to weeks that occurs symmetrically on the cheeks and bridge of the nose, sparing the nasolabial folds.

The malar rash of SLE can be mimicked by: acne, rosacea, seborrheic dermatitis, perioral dermatitis, atopic dermatitis, erysipelas.
Acute cutaneous lupus erythematosus
- The palmar surfaces, dorsa of the hands, and extensor surfaces of the fingers are commonly involved

Gottron’s sign  Reverse Gottron’s sign
Subacute cutaneous lupus erythematosus

Characterized by the presence of nonscarring, photosensitive lesions that can take one of two distinct forms:

- **Papulosquamous** lesions that resemble psoriasis
- **Annular-polycyclic** lesions with peripheral scale and central clearing
SCLE has a predilection for the back, neck, shoulders, and extensor surfaces of the arms and usually spares the face.
Chronic cutaneous lupus erythematosus

These lesions often begin as erythematous papules or plaques, with scaling that may become thick and adherent, with a hypopigmented central area.

As the lesion progresses, follicular plugging occurs, with the development of scarring with central atrophy.
Mucosal ulcers

Mucosal lesions may result in ulcers of the mouth, nose, or genital area or produce nasal septal erosions, which occasionally lead to nasal septal perforation.
Photosensitivity

• Photosensitivity in SLE is defined as *an abnormal cutaneous reaction to ultraviolet radiation*
  • The lesions of LE-specific or LE-non-specific skin disease may be induced or exacerbated by UVR
  • Most abnormal skin reactions occurred 1 to 2 weeks after exposure to light and persisted for weeks to months

• In addition to the skin reaction, patients may develop exacerbations of their systemic disease
Arthritis

- Involvement of the joints either as arthralgias, arthritis, or both is one of the earliest and most common presenting manifestations of SLE
  - Lupus arthritis is characterized by a symmetric, inflammatory arthritis predominantly affecting the knees, wrists, and small joints of the hands
  - Synovial effusions are typically small and not as inflammatory as those present in rheumatoid arthritis
- Deforming arthropathy in systemic lupus erythematosus
  - Non-erosive arthropathy – Jaccoud arthropathy
  - Erosive symmetric polyarthritis with rheumatoid arthritis-like deformities – rhupus
  - Mild deforming arthritis
Jaccoud arthropathy

Deformities are due to lax joint capsules, tendons, and ligaments that cause joint instability

They are initially reversible, but can become fixed due to fibrosis of the joint capsule and ligaments
Jaccoud arthropathy

Radiograph of characteristic joint deviation with MCP subluxation, ulnar deviation, swan-neck deformity of the fingers *without erosions* in Jaccoud's arthropathy
Rhupus
= Rheumatoid arthritis + Systemic lupus erythematosus
Avascular necrosis

- The end result of interruption of the blood supply to bone, leading to reactive hyperemia of adjacent bone, demineralization, and then collapse
- The most commonly affected sites include the femoral heads, tibial plateaus, and femoral condyles
- Smaller joints can be involved as well

Risk factors
- High disease activity
- High doses of glucocorticoids
- Use of cytotoxic medications
Lupus nephritis

Persistent proteinuria
≥0.5 gm per day
or greater than 3+ by dipstick

Cellular casts
including red blood cells, hemoglobin, granular, tubular, or mixed
Indications for renal biopsy

- Increasing serum creatinine without compelling alternative causes
- Proteinuria of $\geq 1.0 \text{ gm per 24 hours}$
- Proteinuria $\geq 0.5 \text{ gm per 24 hours}$, plus hematuria, defined as $\geq 5 \text{ RBCs per hpf}$, or cellular casts
Renal biopsy

- Classify the glomerular disease
- Evaluate for activity and chronicity and for tubular and vascular changes
- Identify additional or alternative causes of renal disease
## Classification of glomerulonephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial LN</td>
<td>Generally do not require immunosuppressive treatment</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative LN</td>
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<tr>
<td>Class III</td>
<td>Focal LN (&lt;50% of glomeruli) III (A): active lesions</td>
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<tr>
<td></td>
<td>III (A/C): active and chronic lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III (C): chronic lesions</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse LN (≥50% glomeruli) Diffuse segmental (IV-S) or global (IV-G) LN IV</td>
<td>Generally require aggressive therapy with glucocorticoids and immunosuppressive agents</td>
</tr>
<tr>
<td></td>
<td>(A): active lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV (A/C): active and chronic lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV (C): chronic lesions</td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous LN</td>
<td>When combined with class III or IV should be treated in the same manner as class III or IV Class V alone may be approached somewhat differently</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual</td>
<td>Generally requires preparation for renal replacement therapy rather than immunosuppression</td>
</tr>
</tbody>
</table>
ISN/RPS Class II
- Mesangial proliferative LN

Mesangial lupus nephritis with accumulation of immune complex deposits within the mesangium (class I) progressing to mesangial hypercellularity (class II) form the milder spectrum of the renal lesions.
ISN/RPS Class III/IV
- Focal/diffuse LN

Depending on the percentage of glomeruli involved with subendothelial deposits, lupus nephritis is further classified as focal (class III; <50% involved) or diffuse (class IV; ≥50% glomeruli involved)
ISN/RPS Class V
- Membranous LN
Membranous lesions (class V) have mainly subepithelial deposits and may have mesangial involvement
Tubulointerstitial disease

Observed in up to 66% of SLE renal biopsy specimens

Characterized by inflammatory cell infiltrates, tubular damage, and interstitial fibrosis

A strong predictor of poor long-term renal outcome
Pathologic diagnosis:
Kidney, needle biopsy --- Membranous lupus glomerulonephritis, INS/RPS class V. and mild chronic interstitial fibrosis/tubular atrophy.

Ancillary study for diagnosis:
1. PAS, PASM and Masson trichrome stains done.
2. IgG and C4d IHC stains done.

Prognostic and predictive factor:
1. **Activity index: 0/24** (cellular crescent: 0; necrotizing lesion: 0; endocapillary proliferation: 0; wire loop: 0; neutrophils infiltration: 0; interstitial inflammation: 0).
2. **Chronicity index: 2/12** (global obsolete glomeruli: 0; tubular atrophy: 1; interstitial fibrosis: 1; fibrous crescent: 0).
## Activity and chronicity indices for lupus nephritis

<table>
<thead>
<tr>
<th></th>
<th><strong>Activity</strong></th>
<th><strong>Chronicity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glomerular lesions</strong></td>
<td>Proliferation</td>
<td>Sclerotic glomeruli</td>
</tr>
<tr>
<td></td>
<td>Necrosis/karyorrhexis</td>
<td>Fibrous crescents</td>
</tr>
<tr>
<td></td>
<td>Hyaline thrombi</td>
<td></td>
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<tr>
<td></td>
<td>Cellular crescents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocytic exudation</td>
<td></td>
</tr>
<tr>
<td><strong>Tubulointerstitial lesions</strong></td>
<td>Mononuclear cell infiltration</td>
<td>Tubular atrophy</td>
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<tr>
<td></td>
<td>Interstitial fibrosis</td>
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</table>
High-risk histologic features associated with worse renal prognosis

**Cellular crescents**

**Interstitial fibrosis**
Renal vascular lesions in SLE

- Lupus vasculopathy
  - Presence of immunoglobulin and complement-containing hyaline thrombi within the glomerular capillary or arteriolar lumina

- Thrombotic microangiopathy
  - Presence of fibrin thrombi within the glomerular capillary or arteriolar lumina
  - May be associated with the presence of antiphospholipid antibodies

- Vasculitis
  - Characterized by leukocyte infiltration and fibrinoid necrosis of arterial walls

- Nonspecific vascular sclerosis
  - Commonly observed and characterized by fibrous intimal thickening
Renal vascular lesions in SLE

Renal vascular lesions are common in SLE patients with nephritis and may be associated with arterial vascular events.

Lupus vasculopathy - Inflammatory changes to the vascular wall are absent

Nonspecific sclerotic vascular lesions - characterized by fibrous intimal thickening

TMA - characterized by the presence of fibrin thrombi within the glomerular capillary or arteriolar lumina

Neuropsychiatric manifestations
- ACR classification of neuropsychiatric syndromes in systemic lupus erythematosus

- **Central nervous system**
  - Acute confusional state
  - Cognitive dysfunction
  - Psychosis
  - Mood disorder
  - Anxiety disorder
  - Headache
  - Cerebrovascular accident
  - Myelopathy
  - Movement disorder
  - Demyelinating syndrome
  - Seizure disorder
  - Aseptic meningitis

- **Peripheral nervous system**
  - Cranial neuropathy
  - Polyneuropathy
  - Plexopathy
  - Mononeuropathy, single/multiplex
  - Guillain-Barré syndrome
  - Myasthenia gravis
  - Autonomic disorder
Neuropsychiatric manifestations

• Central nervous system
  • Acute confusional state
  • Cognitive dysfunction
  • Psychosis
  • Mood disorder
  • Anxiety disorder
  • Headache
  • Cerebrovascular accident
  • Myelopathy
  • Movement disorder
  • Demyelinating syndrome
  • Seizure disorder
  • Aseptic meningitis

Headache

• Intractable headaches, unresponsive to narcotic analgesics, are the most common feature of neurologic disease in patients with lupus
• Active migraine headaches are associated with
  • Higher disease activity scores
  • Worsening of Raynaud phenomenon
  • Presence of antiphospholipid antibodies
• Headaches may also be secondary to increased intracranial pressure or cerebral vein thrombosis
Neuropsychiatric manifestations

- Central nervous system
  - Acute confusional state
  - Cognitive dysfunction
  - Psychosis
  - Mood disorder
  - Anxiety disorder
  - Headache
  - Cerebrovascular accident
  - Myelopathy
  - Movement disorder
  - Demyelinating syndrome
  - Seizure disorder
  - Aseptic meningitis

Cerebrovascular accident

- The major period for risk of stroke is within the first 5 years of diagnosis of SLE
- Patients with a history of transient ischemic attacks or cardiac valvular lesions are at high (57% and 87%, respectively) risk of stroke
- The risk for recurrent CVA is increased in patients who have had a CVA before (64%)
- Younger SLE patients are at increased risk for CVA when compared with an age-matched population

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Neuropsychiatric manifestations

• Central nervous system
  • Acute confusional state
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  • Myelopathy
  • Movement disorder
  • Demyelinating syndrome
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Transverse myelitis

• Myelitis is characterized by the onset of bilateral lower extremity paresthesia, numbness, and weakness that can rapidly progress to involve the upper limbs and the muscles of respiration
  • Sensory level
  • Autonomic involvement of the bowel and bladder
• Even with prompt diagnosis and aggressive treatment, complete recovery is seen in 50% of the patients, partial recovery in 29%, and worsening or no improvement in 21%
• Bladder abnormalities tend to persist even after motor recovery in these patients
Neuropsychiatric manifestations

• Central nervous system
  • Acute confusional state
  • Cognitive dysfunction
  • Psychosis
  • Mood disorder
  • Anxiety disorder
  • Headache
  • Cerebrovascular accident
  • Myelopathy
  • Movement disorder
  • Demyelinating syndrome
  • Seizure disorder
  • Aseptic meningitis

Seizure disorder

• Generalized tonic-clonic seizures occur much more frequently and are associated with active SLE disease
  • Focal seizures may recur at any time irrespective of disease activity
  • The risk of seizures is increased in those patients with
    • Higher disease activity at baseline
    • Prior neuropsychiatric disease
    • Anti-Smith and anti-cardiolipin antibodies
    • Fifty percent of seizures are due to concomitant infections, metabolic derangements, or iatrogenic complications
Autopsy findings in a patient with cerebral vasculitis

Many of the manifestations can be grouped into two broad categories:

• Primary vascular injury
• Primary inflammatory injury

True vasculitis of cerebral vessels is rare

• Neuropathologic findings include widely scattered, multifocal infarcts characterized by ...
  • Fibrinoid necrosis of small intracortical arterioles and capillaries
  • Petechial hemorrhage
  • Parenchymal necrosis with variable glial reaction
  • Vascular endothelial cell proliferation
Approach to neuropsychiatric manifestations
- 2010 EULAR recommendations

• What are the risk factors for neuropsychiatric SLE?
  • Generalized (non-CNS) lupus activity or damage
  • Previous or other concurrent major neuropsychiatric SLE manifestation(s)
  • Persistently positive moderate-to-high titers of aPL antibodies

• When to suspect neuropsychiatric SLE
  • Any SLE patient at risk who presents with new-onset neurologic or psychiatric manifestations without an apparent cause
  • In patients with subtle or mild signs or symptoms, a high index of suspicion is required to exclude underlying overt neuropsychiatric SLE
• Is it neuropsychiatric SLE?
  • Mild manifestations (headache, mood disorders, anxiety, mild cognitive dysfunction, polyneuropathy without electrophysiologic confirmation) are common (up to 40%) but are not usually related to lupus
  • Non-SLE-related causes (infections, metabolic disturbances, drug adverse effects) must be excluded
  • Most (40%-50%) lupus-related events occur at onset or during the first 2-4 yr after SLE diagnosis, common (50%-60%) in the presence of generalized lupus activity
  • Attribution to lupus more likely when neuropsychiatric SLE risk factors are present

• What diagnostic workup is indicated?
Diagnostic tests in neuropsychiatric manifestations

• MRI
  - *The preferred imaging modality*
  - Help to identify ischemic/thrombotic, demyelinating, or infectious processes
  - May reflect underlying CNS lupus activity
    - Small, hyperintense, T2-weighted, focal white matter lesions located in the periventricular and subcortical white matter of the frontoparietal region of the brain

• CSF study
  - Non-specific CSF abnormalities such as increased cell count, increased protein, or reduced glucose may be present in about one third of patients
  - Increases in IgG, IgA, or IgM indices have been described in patients with CNS lupus and proposed as evidence of CNS disease activity
  - Electroencephalogram
  - Neuropsychologic tests
  - Nerve conduction studies
Gastrointestinal involvement

• Lupus enteritis
• Mesenteric vasculitis or thrombosis
• Peritonitis
Lupus enteritis

It is characterized by bowel wall thickening, dilated bowel loops, and abnormal bowel wall enhancement (double-halo or target sign) and is thought to be caused by vasculitis of the bowel wall.

The most commonly affected areas are the jejunum and ileum.
Liver test abnormalities
- Occur in up to 60% of SLE patients at some point during the course of their illness

• Clinically significant liver disease is rarely a direct manifestation of SLE
  • Medications – NSAIDs, methotrexate, and azathioprine
  • Infections – viral hepatitis, cytomegalovirus (CMV), and Epstein-Barr virus (EBV)
  • Lupus hepatitis
    • Typically characterized by the presence of lobular inflammation with a paucity of lymphoid infiltrates
    • In contrast with autoimmune hepatitis – dominant periportal (interface) inflammation and dense lymphoid infiltrates
  • Nodular regenerative hyperplasia – diffuse nodularity of the liver with little fibrosis
  • Vascular disorders – Budd-Chiari syndrome, hepatic veno-occlusive disease, and hepatic infarction (especially in the setting of antiphospholipid antibodies)
Ophthalmologic involvement

- Keratoconjunctivitis sicca (KCS)
  - The most common ocular manifestation
- SLE retinopathy
  - An immune complex-mediated vasculopathy and/or the result of microthrombotic events
  - Correlate with lupus nephritis, CNS lupus, and the presence of antiphospholipid antibodies
- Episcleritis and scleritis
- Complications of therapy
  - Glucocorticoids – posterior subcapsular cataracts and elevated intraocular pressure
  - Antimalarial agents – maculopathy
Hematologic abnormalities

- **Anemia**
  - Anemia of chronic disease
  - Iron-deficiency anemia
  - Autoimmune hemolytic anemia (AIHA)
    - Increased serum unconjugated bilirubin, increased lactate dehydrogenase (LDH), increased reticulocyte count, and reduced serum haptoglobin
    - Positive direct Coombs’ test
    - Spherocytosis on peripheral blood smear
  - Other causes of anemia, such as medications, infections, and microangiopathic hemolytic anemia, must be ruled out
Peripheral blood smear

**Spherocytes**
- in autoimmune hemolytic anemia

**Schistocytes**
- in microangiopathic hemolytic anemia
Hematologic abnormalities

• Leukopenia
  • The white blood cell count rarely decreases to less than 1500/mm$^3$ in active SLE, unless there is an additional cause
    • Neutropenia itself in SLE patients is usually the result of immunosuppressive agents
    • Lymphocytopenia is usually associated with antibodies to lymphocytes and is associated with active SLE
  • Other causes of leukopenia, such as medications and infections, must be ruled out
Hematologic abnormalities

- Thrombocytopenia
  - Thrombocytopenia can be the result of immune-mediated platelet destruction similar to immune thrombocytopenic purpura (ITP)
    - Ninety-one percent of SLE patients with thrombocytopenia have autoantibodies to either TPOR or GPIIb/IIIa
    - SLE-related thrombocytopenia occurring with autoimmune hemolytic anemia (Evan syndrome) is associated with the presence of antiphospholipid antibodies
  - Antiphospholipid syndrome
    - In some instances of refractory thrombocytopenia with SLE, often without platelet antibodies, the antiphospholipid antibody syndrome should be suspected
  - Thrombotic thrombocytopenic purpura
    - TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, CNS deficits, renal dysfunction, and fever
  - Other causes of thrombocytopenia, such as medications and infections, must be ruled out
• Pancytopenia
  • Pancytopenia in SLE may result from the disease itself, the effects of drugs, and infections
  • *Hemophagocytic syndrome*

• Lymphadenopathy
  • Reactive hyperplasia with varying degrees of coagulative necrosis
  • Infection or a lymphoproliferative process should be ruled out
Pulmonary involvement

- Pleuritis and pleural effusion
- Pneumonitis and chronic interstitial lung disease
- Pulmonary arterial hypertension
- Pulmonary hemorrhage
  - Diffuse alveolar hemorrhage is a life-threatening manifestation of SLE that occurs in less than 2% of patients
  - The characteristic presentation is abrupt onset of dyspnea, cough, fever, infiltrates and a dramatic fall in hemoglobin
  - Hemoptysis is present in only 50% of the cases
  - Bronchoscopy with bronchoalveolar lavage is a major tool for diagnosing diffuse alveolar hemorrhage and excluding infection
Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage is usually due to a vasculitis with pulmonary capillaritis and a distinctive small-vessel vasculitis of the arterioles and small muscular pulmonary arteries.
Cardiac manifestations

• Pericarditis and pericardial effusion
• Myocarditis
• Endocarditis
  • **Libman-Sacks endocarditis** – pea-sized, flat or raised, granular lesions that occur most commonly on the ventricular aspects of the mitral valve posterior leaflet
• Valvular abnormalities
  • Increased incidence (22% vs 15%) of stroke, peripheral embolism, congestive heart failure, infective endocarditis, need for valve replacement, and death
Accelerated atherosclerosis

- Patients in the 35- to 44-year age group were more than 50 times more likely to have a myocardial infarction than women of similar age.
- There is an increase in both traditional and non-traditional risk factors for atherosclerosis in SLE patients:
  - Traditional risk factors – Hypertension, diabetes mellitus, metabolic syndrome, and dyslipidemia.
  - Non-traditional risk factors – Renal failure, higher levels of oxidized low-density lipoproteins, and premature ovarian failure.
Diagnosis
# Criteria for the classification of SLE

- 1997 update of the 1982 revised ACR classification criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malar rash</strong></td>
<td>Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds</td>
</tr>
<tr>
<td><strong>Discoid rash</strong></td>
<td>Erythematous raised patches with adherent keratotic scale and follicular plugging; atrophic scarring may occur in older lesions</td>
</tr>
<tr>
<td><strong>Photosensitivity</strong></td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
</tr>
<tr>
<td><strong>Oral ulcers</strong></td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>Nonerosive arthritis involving two or more peripheral joints</td>
</tr>
<tr>
<td><strong>Serositis</strong></td>
<td>a. Pleuritis—convincing history of pleuritic chest pain or rub heard by a physician or evidence of pleural effusions or b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion</td>
</tr>
<tr>
<td><strong>Renal disorder</strong></td>
<td>a. Persistent proteinuria &gt;0.5 g/day, &gt;3+ if quantification not performed or b. Cellular casts: may be red blood cell, hemoglobin, granular tubular, or mixed</td>
</tr>
<tr>
<td><strong>Neurologic disorder</strong></td>
<td>a. Seizures: in the absence of offending drugs or known metabolic derangements or b. Psychosis: in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td><strong>Hematologic disorder</strong></td>
<td>a. Hemolytic anemia with reticulocytosis or b. Leukopenia &lt;4000/mm3 or c. Lymphopenia &lt;1500/mm3 or d. Thrombocytopenia &lt;100,000/mm3 in the absence of offending drugs</td>
</tr>
<tr>
<td><strong>Immunologic disorder</strong></td>
<td>a. Anti-DNA: antibody to native DNA in abnormal titer or b. Anti-Smith: presence of antibody to Sm nuclear antigen or c. Positive finding of antiphospholipid antibodies</td>
</tr>
<tr>
<td><strong>Positive ANA</strong></td>
<td>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 syndromes</td>
</tr>
</tbody>
</table>
Serologic tests

• The hallmark serologic feature is the presence of ANA
  • Highly sensitive and is positive in more than 95% of people with SLE
  • Positive ANA tests also occur in many other autoimmune diseases
  • ANAs are also detectable in low titers (<1 : 80) in many people without autoimmune disease, especially in the elderly
Serologic tests

• The hallmark serologic feature is the presence of ANA
  • Highly sensitive and is positive in more than 95% of people with SLE
  • Positive ANA tests also occur in many other autoimmune diseases
  • ANAs are also detectable in low titers (<1 : 80) in many people without autoimmune disease, especially in the elderly

A positive test is not sufficient to establish the diagnosis of SLE
A negative test can be helpful in ruling out SLE
Autoantibodies and clinical significance in systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Prevalence</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-dsDNA</td>
<td>60%</td>
<td>95% specificity for SLE; fluctuates with disease activity; associated with glomerulonephritis</td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>20%-30%</td>
<td>99% specificity for SLE; associated with anti-U1RNP antibodies</td>
</tr>
<tr>
<td>Anti-U1RNP</td>
<td>30%</td>
<td>Antibody associated with mixed connective tissue disease and lower frequency of glomerulonephritis</td>
</tr>
<tr>
<td>Anti-Ro/SSA</td>
<td>30%</td>
<td>Associated with Sjögren’s syndrome, photosensitivity, SCLE, neonatal lupus, congenital heart block</td>
</tr>
<tr>
<td>Anti-La/SSB</td>
<td>20%</td>
<td>Associated with Sjögren’s syndrome, SCLE, neonatal lupus, congenital heart block, anti-Ro/SSA</td>
</tr>
<tr>
<td>Antihistone</td>
<td>70%</td>
<td>Also associated with drug-induced lupus</td>
</tr>
<tr>
<td>Antiphospholipid</td>
<td>30%</td>
<td>Associated with arterial and venous thrombosis, pregnancy morbidity</td>
</tr>
</tbody>
</table>
Differential diagnosis

• Viral infections
  • Parvovirus B19
    • Fever, rash, symmetric inflammatory polyarthritis, and cytopenias
    • Presence of ANA, anti-dsDNA, and hypocomplementemia
  • Cytomegalovirus and Epstein-Barr virus
    • Fatigue, cytopenias, abdominal pain, and liver test abnormalities
  • Acute HIV infection
    • Fever, diffuse lymphadenopathy, and oral ulcers
• Hepatitis B and C
  • Inflammatory arthritis
  • Positive autoantibodies
Differential diagnosis

• Malignancy
  • Non-Hodgkin’s lymphoma
    • Constitutional symptoms, joint pain, cytopenias, lymphadenopathy, rash
    • Positive ANA
  • Paraneoplastic syndrome

• Other autoimmune diseases
  • Rheumatoid arthritis
  • Adult-onset Still’s disease
  • Dermatomyositis
  • Mixed connective tissue disease
Differential diagnosis

- Drug-induced lupus – *minocycline, procainamide, hydralazine, isoniazid, interferon alpha*, and *anti-TNF agents*
  - Arthralgia, myalgia, fever, and serositis
  - Positive ANA
  - Antihistone antibodies
    - Present in more than 95% of cases of drug-induced lupus
    - Up to 80% of idiopathic SLE patients will also produce antihistone antibodies
Assessment of Disease Activity
Systemic approach to assessment

- There is more to lupus than the American College of Rheumatology (ACR) criteria
  - Patients should be assessed from head to foot, with both history taking and physical examination
- Whatever feature is being considered
  - How long it has been present, whether it has occurred before, and if so, whether it resolved spontaneously or as a result of a particular intervention
    - Is it currently getting worse, getting better, or stable?
  - Whether or not the feature is likely to be due to active lupus, a complication of lupus, or other comorbid disease
  - It is necessary to determine the circumstances around and prior to the onset of the lupus flare
    - Was the patient exposed to sunlight?
    - Did he or she suffer an infection?
    - Was the patient's therapy reduced?
Use of laboratory tests in the assessment of disease activity

• Complete blood count with white count differential

• Renal assessment
  • Urine dipstick
  • Microscopic examination
  • 24-hour urine protein or random urine protein/creatinine ratio
  • Calculated creatinine clearance and glomerular filtration rate
  • Renal biopsy

• Serologic tests
  • Anti-dsDNA antibodies
  • C3 and C4 levels

• CSF study
Recording of disease activity

• Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)
• British Isles Lupus Assessment Group (BILAG) index
• System Lupus Activity Measure (SLAM)
• European Consensus Lupus Activity Measure (ECLAM)
**SLEDAI 2000**

*Enter the weighted score for each descriptor if the descriptor was present at the time of the visit or in the preceding 10 days*

<table>
<thead>
<tr>
<th>Score</th>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Seizure</td>
<td>Recent onset. Exclude metabolic, infectious, or drug-related causes.</td>
</tr>
<tr>
<td>8</td>
<td>Psychosis</td>
<td>Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized, or catatonic behavior. Exclude the presence of uremia and offending drugs.</td>
</tr>
<tr>
<td>8</td>
<td>Organic brain syndrome</td>
<td>Altered mental function with impaired orientation or impaired memory or other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, and increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug-related causes.</td>
</tr>
<tr>
<td>8</td>
<td>Visual</td>
<td>Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection).</td>
</tr>
<tr>
<td>8</td>
<td>Cranial nerve</td>
<td>New onset of a sensory or motor neuropathy involving cranial nerves.</td>
</tr>
<tr>
<td>8</td>
<td>Lupus headache</td>
<td>Severe, persistent headache; may be migrainous; but must be unresponsive to narcotic analgesia.</td>
</tr>
<tr>
<td>8</td>
<td>Cerebrovascular accident</td>
<td>New-onset cerebrovascular accident(s). Exclude arteriosclerosis.</td>
</tr>
<tr>
<td>8</td>
<td>Vasculitis</td>
<td>Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.</td>
</tr>
<tr>
<td>4</td>
<td>Arthritis</td>
<td>≥2 joints with pain and signs of inflammation (e.g., tenderness, swelling, or effusion).</td>
</tr>
<tr>
<td>4</td>
<td>Proteinuria</td>
<td>More than 0.5 gm of urinary protein excreted per 24 hr.</td>
</tr>
<tr>
<td>4</td>
<td>Pyuria</td>
<td>More than 5 leukocytes per high-power field. Exclude infection.</td>
</tr>
<tr>
<td>2</td>
<td>Rash</td>
<td>Inflammatory-type rash.</td>
</tr>
<tr>
<td>2</td>
<td>Alopecia</td>
<td>Abnormal, patchy, or diffuse loss of hair.</td>
</tr>
<tr>
<td>2</td>
<td>Mucosal ulcers</td>
<td>Oral or nasal ulcerations.</td>
</tr>
<tr>
<td>2</td>
<td>Pleurisy</td>
<td>Pleuritic chest pain with pleural rub or effusion, or pleural thickening.</td>
</tr>
<tr>
<td>2</td>
<td>Pericarditis</td>
<td>Pericardial pain with ≥1 of the following: rub, electrocardiography, or echocardiogram confirmation.</td>
</tr>
<tr>
<td>2</td>
<td>Low complement</td>
<td>Decrease in CH50, C3 or C4 level (to less than the lower limit of normal for testing laboratory)</td>
</tr>
<tr>
<td>2</td>
<td>Increased DNA binding</td>
<td>Increased DNA binding above the normal range for testing laboratory.</td>
</tr>
<tr>
<td>1</td>
<td>Fever</td>
<td>More than 38 °C. Exclude infectious cause.</td>
</tr>
<tr>
<td>1</td>
<td>Thrombocytopenia</td>
<td>&lt;100 × 10^9 platelets/L, exclude drug causes.</td>
</tr>
<tr>
<td>1</td>
<td>Leukopenia</td>
<td>Leukocyte count &lt;3 × 10^9/L, exclude drug causes.</td>
</tr>
</tbody>
</table>
## SLICC/ACR damage index
- Features must be present for 6 months to be recorded

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular (either eye, by clinical assessment)</strong></td>
<td></td>
</tr>
<tr>
<td>Any cataract ever</td>
<td>1</td>
</tr>
<tr>
<td>Retinal change or optic atrophy</td>
<td>1</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) or major psychosis</td>
<td>1</td>
</tr>
<tr>
<td>Seizures requiring therapy for 6 mo</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident ever (score 2 if &gt; 1)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Cranial or peripheral neuropathy (excluding optic)</td>
<td>1</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Estimated or measured glomerular filtration rate &lt;50%</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria &gt;3.5 gm/24 hr</td>
<td>1</td>
</tr>
<tr>
<td>or End-stage renal disease (regardless of dialysis or transplantation)</td>
<td>or 3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension (right ventricular prominence, or loud P2)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fibrosis (physical and radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pleural fibrosis (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary infarction (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Angina or coronary artery bypass</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction ever (score 2 if &gt;1)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Cardiomyopathy (ventricular dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis for 6 mo, or pericardietectomy</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td></td>
</tr>
<tr>
<td>Claudication for 6 mo</td>
<td>1</td>
</tr>
<tr>
<td>Minor tissue loss (pulp space)</td>
<td>1</td>
</tr>
<tr>
<td>Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if &gt;1 site)</td>
<td>1</td>
</tr>
<tr>
<td>Venous thrombosis with swelling, ulceration, or venous stasis</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Infarction or resection of bowel below duodenum, spleen, liver, or gallbladder ever, for cause (score 2 if &gt;1 site)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Mesenteric insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Chronic peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Stricture or upper gastrointestinal tract surgery ever</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic insufficiency requiring enzyme replacement</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Muscle atrophy or weakness</td>
<td>1</td>
</tr>
<tr>
<td>Deforming or erosive arthritis (including reducible deformities excluding avascular necrosis)</td>
<td>1</td>
</tr>
<tr>
<td>Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)</td>
<td>1</td>
</tr>
<tr>
<td>Avascular necrosis (score 2 if &gt;1)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1</td>
</tr>
<tr>
<td>Tendon rupture</td>
<td>1</td>
</tr>
<tr>
<td>Skin and other</td>
<td></td>
</tr>
<tr>
<td>Scarring chronic alopecia</td>
<td>1</td>
</tr>
<tr>
<td>Extensive scarring of panniculum other than scalp and pulp space</td>
<td>1</td>
</tr>
<tr>
<td>Skin ulceration (excluding thrombosis for &gt;6 mo)</td>
<td>1</td>
</tr>
<tr>
<td>Premature gonadal failure</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (regardless of treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (exclude dysplasia) (score 2 if &gt;1 site)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>
Treatment
Drugs used in the treatment of systemic lupus erythematosus

- **Glucocorticoids**
  - Used when other initial therapies (antimalarials) are not tolerated or are inadequate to control disease activity
  - As either single or background therapy in combination with immunosuppressive agents in moderate to severe disease
  - As pulse therapy in severe, rapidly progressing disease or when doses greater than 0.6 mg/kg/day prednisone equivalent are required to control disease activity

- **Antimalarials**
  - Effective for skin and mucocutaneous manifestations
  - Adjunctive therapy of severe lupus and to prevent flares
Drugs used in the treatment of systemic lupus erythematosus

• Azathioprine
  • Effective as an induction and a maintenance regimen in mild to moderate SLE including nephritis

• Cyclophosphamide
  • The standard of care for severe SLE with major organ involvement

• MMF
  • At least equally efficacious and has a better toxicity profile than cyclophosphamide in the treatment of moderately severe proliferative lupus nephritis
Drugs used in the treatment of systemic lupus erythematosus

• Calcineurin inhibitors
  • Used alone or in combination with other immunosuppressive agents in lupus nephritis refractory to cytotoxic therapy

• Rituximab
  • A therapeutic option for selected cases of lupus nephritis refractory to conventional immunosuppressive treatment
Management of cutaneous manifestations

Skin manifestations in SLE usually respond to:

- *Sun exposure prophylaxis*
- *Topical glucocorticoids*
- *Systemic antimalarials*
Management of proliferative lupus nephritis

Severity of proliferative lupus nephritis:

*Mild*
- Class III nephritis without severe histologic features (crescents, fibrinoid necrosis); low chronicity index (≤3); normal renal function; non-nephrotic range proteinuria

*Moderately severe*
- Mild disease as defined above with partial or no response after the initial induction therapy, or delayed remission (>12 mo), or
- Focal proliferative nephritis with adverse histologic features or reproducible SCr increase ≥30%, or
- Class IV nephritis without adverse histologic features

*Severe*
- Moderately severe as defined above but not remitting after 6-12 mo of therapy, or
- Proliferative disease with impaired renal function and fibrinoid necrosis or crescents in >25% of glomeruli, or
- Mixed membranous and proliferative nephritis, or
- Proliferative nephritis with high chronicity alone (chronicity index >4) or in combination with high activity (chronicity index >3 and activity index >10), or
- Rapidly progressive glomerulonephritis (doubling of SCr within 2-3 mo)
Management of neuropsychiatric SLE

• Control aggravating factors
  • Infection, dehydration, metabolic abnormalities, hypertension

• Control symptoms
  • Anticonvulsants, antidepressants, antipsychotics

• Glucocorticoids and/or immunosuppressive therapy
  • Acute confusional state, aseptic meningitis, myelitis, optic neuritis, refractory seizure disorder, peripheral neuropathies, severe psychosis
  • Generalized (non-CNS) lupus activity

• Antithrombotic or antiplatelet therapy
  • aPL-associated neuropsychiatric SLE (particularly cerebrovascular disease, ischemic optic neuropathy, chorea)
  • Antiphospholipid syndrome-associated thrombotic events
Management of hematologic disease

• Regular monitoring for mild cytopenia
• Glucocorticoids (1 mg/kg/day with gradual tapering) are the mainstay of treatment for more severe cases (platelet count < 50x10^3/mm^3 or active bleeding, neutrophil count <1000/mm^3)
  • Pulses of IV-MP followed by lower doses of prednisone
  • Steroid-sparing agents (azathioprine, cyclosporine)
• Splenectomy in steroid-resistant thrombocytopenia
• For resistant life-threatening cytopenia
  • Monthly pulses of IV cyclophosphamide
  • Rituximab
  • IVIG
  • Thrombopoietin mimetic agents (romiplostim and eltrombopag) for immune thrombocytopenia

• Supportive treatment
  • Broad-spectrum antibiotics and G-CSF in febrile neutropenia
  • Red blood cell transfusions in serious hemolytic anemia (Hb < 7 g/dL)
  • Platelet transfusions if invasive procedures are planned
Antiphospholipid syndrome

Previous thrombosis

Yes

Proximal deep vein thrombosis or pulmonary embolism

Warfarin (INR 2.0-3.0)

No transient risk factor: long term anticoagulation
Transient/reversible risk factor: 3-6 months

Cardioembolic

Warfarin (INR 2.0-3.0)

Non-cardioembolic

Non-cerebral

Aspirin + clopidogrel ± dipyridamole

Arterial thrombosis

Cerebral

Therapeutic low molecular weight heparin ± monitor anti-FX

Change to warfarin (INR 2.0-3.0) postpartum

Pregnant

Yes

Previous pregnancy morbidity satisfying antiphospholipid syndrome classification criteria

No treatment

No

No

Non-cardiac

Warfarin (INR 2.0-3.0)

Recurrent episode while receiving warfarin

Warfarin (INR 3.0-4.0) or warfarin (INR 2.0-3.0) + low dose aspirin or if unstable INR low molecular weight heparin

No treatment
Management of pregnancy in systemic lupus erythematosus

- Planning of pregnancy
  - Ensure that lupus is inactive for at least 6 months
  - Reassure patient: small risk for major flare
  - Discourage pregnancy if SCr >2 mg/dL

- Determine aPL antibodies and other antibodies that may be of relevance (anti-SSA, anti-SSB), and obtain baseline serology and chemistry labs

- Monitor closely blood pressure and proteinuria
  - Presence of generalized lupus activity, active urine sediment, and low serum complement are in favor of lupus nephritis

- For patients with antiphospholipid syndrome, consider combined heparin and aspirin to reduce risk for pregnancy loss and thrombosis
  - Patients with aPL antibodies may be treated with aspirin, although there are no adequate data to support its use
The risks of treatment with potential deleterious effects on the mother and the fetus must be balanced against the risks of untreated disease.

- **Glucocorticoids**
  - In mild flares involving the skin, joints, and blood
  - A small risk of harm (increased risk of cleft palate in children, intrauterine growth retardation, maternal hypertension, diabetes)

- **Antimalarials**
  - Good safety record despite crossing the placenta

- **Azathioprine (category D) and cyclosporine (category C)**
  - Can be used with caution as a steroid-sparing agent
• Cyclophosphamide
  • A major teratogen
  • Should not be used unless there is no available alternative for organ-threatening disease in the mother
  • Fetal loss due to cyclophosphamide toxicity may occur
• MMF (category D), methotrexate (category X), and biologic agents
  • Should be avoided

For pregnant SLE patients with a severe renal flare

• High-dose glucocorticoids
• Azathioprine as a steroid-sparing agent
• Prompt delivery of the fetus at the earliest safe time point possible
• Breastfeeding
  • Nursing is permissible for women receiving glucocorticoids
    • The interval between dose and nursing should be at least 4 hours if the prednisone dosage is greater than 20 mg/day
  • Antimalarials may be continued during lactation
  • Azathioprine is not recommended
    • Possible risk for immunosuppression, carcinogenicity, and growth restriction of the child
  • Methotrexate, leflunomide, cyclosporine, MMF, and cyclophosphamide are contraindicated
Management of SLE patients who receive immunosuppressive therapy and present with fever

* Comorbidities
  - Age older than 65 years
  - Diabetes
  - Chronic cardiopulmonary disease