A Specialty Networks Company

CLINICAL PRACTICE GUIDELINE

Systemic Lupus Erythematosus (SLE)

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Abbreviations

ACE	Angiotensin-converting-enzyme
ACR	American College of Rheumatology
ALMS	Aspreva Lupus Management Study
ANA	Antinuclear antibody
Anti-dsDNA	Anti-double stranded deoxyribonucleic acid
Anti-Sm	Anti-Smith
Anti-β2GP1	Anti-β2-glycoprotein 1
aPL	Antiphospholipid
BILAG	British Isles Lupus Assessment
BLyS	B-lymphocyte stimulator (also known as BAFF)
BMD	Bone mineral density
BMI	Body mass index
C3	Complement component 3
C4	Complement component 4
CAPS	Catastrophic antiphospholipid syndrome
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CNI	Calcineurin inhibitor
CNS-SLE	Neuropsychiatric lupus
CRP	C-reactive protein
DHEA	Dihydroepiandrosterone
DILE	Drug-induced lupus erythematosus
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
ECLAM	European Consensus of Lupus Activity Measurement
EEG	Electroencephalogram
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
GPL	G-phospholipids
HBV	Hepatitis B virus
HDL	High-density lipoprotein
HPV	Human papillomavirus
ICD	intrauterine contraceptive device
IFN	Interferon
IV	Intravenous

LFT	Liver function test
LLDAS	Lupus Low Disease Activity State
LMW	Low molecular weight
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
NSAID	Nonsteroidal anti-inflammatory drug
Pap	Papanicolaou

PGA	Physician's Global Assessment
RA	Rheumatoid arthritis
RBCs	Red blood cells
REMS	Risk Evaluation Management Strategy
RNP	Ribonucleoprotein
RPR	Rapid plasma reagin
SLE	Systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SRI	Systemic Lupus Erythematosus Responder Index
SSA	Sjögren's syndrome-related antigen A
SSB	Sjögren's syndrome-related antigen B
TNF	Tumor necrosis factor
US	United States

Introduction

Systemic lupus erythematosus (SLE) is an incurable systemic autoimmune disease with a wide variety of clinical manifestations, ranging from subtle symptoms to life-threatening multi-organ failure. Systemic lupus erythematosus is characterized by alterations in both the innate and adaptive immune systems, ultimately leading to loss of self-tolerance and formation of autoantibodies against nuclear material. The severity of the disease is very variable and characterized by continuous activity, flares or rare periods of remission or near remission.[1]

Recently, four United States (US) regions have reported the incidence of SLE to be between 4.6 and 5.5 per 100 000,[2-6] and a prevalence between 62.2 and 96.8 per 100 000.[7-9] Systemic lupus erythematosus predominantly affects adults, at a female-to-male ratio of between 9:1 and 15:1.[10] It usually affects women of childbearing age (20 to 40 years old). Children and older adults, such as postmenopausal women, can also be affected by the disease. In all studies the prevalence in African-Americans is higher. The incidence of SLE has nearly tripled in the last 4 to 5 decades, largely as a result of earlier detection of mild disease.[7, 10-13] There are probably 300 000 patients with SLE in the US and another 300 000 with purely cutaneous lupus, 10% of whom progress to SLE.[2-4] The survival of patients with SLE has dramatically improved during the last 50 years. The 5-year survival rates were approximately 50% in the 1950s; they range from 88% to 96% today.[14, 15]

The pathogenesis of the immune alterations in SLE is complex.[16-18] Its causes, development, heterogeneous presentation, and unpredictable course make SLE a major diagnostic challenge even for rheumatologists.[19] It is thought that a complex genetic predisposition; environmental triggers; and hormonal factors contribute to the etiology of this disease.[20] According to Rhodes and Vyse (Page 550),[21] "There is a growing understanding that susceptibility to SLE is due to a complex interaction of multiple genes and environmental factors, and that many of these may be shared with other autoimmune diseases."

Studies have shown that more than 80 genes are associated with SLE. When genetically susceptible individuals are exposed to certain environmental and hormonal factors, the disease can develop.[22] The genetic contribution to the development of the disease is supported by the study of twins. In 1992, Deapen et al.[23] published a study of 107 pairs of twins with SLE and found that 24% of the monozygotic twins, but only 2% of dizygotic twins were concordant. First-degree relatives of a patient with SLE have a greater chance of developing SLE.[24]

Environmental factors that are thought to increase the risk for development of SLE in susceptible individuals include but are not limited to the following:[25]

- Ultraviolet light[26]
- Epstein Barr virus[27, 28]
- Smoking
- Silica[29]
- Mercury [30]
- Pesticides[30]

The clinical presentation of SLE is extremely variable. Some of the more recognized presenting manifestations include:[31, 32]

- Fever
- Photosensitive skin rashes
- Alopecia
- Arthralgias and arthritis
- Anemia (hemolytic or anemia of chronic inflammation)
- Leukocytopenia
- Thrombocytopenia
- Renal disease (lupus nephritis)
- Psychosis
- Seizures
- Encephalopathy
- Myelitis
- Serositis including pleuritis and pericarditis
- Arterial or venous thrombosis

As indicated above, SLE is an autoimmune disease associated with auto-antibodies. Some of the common auto-antibodies found in these patients include:[33, 34]

- Antinuclear antibodies (ANA)
- Anti-double stranded deoxyribonucleic acid (anti-dsDNA)
- Anti-Ro (SSA, Sjögren's syndrome-related antigen A) antibodies
- Anti-La (SSB, Sjögren's syndrome-related antigen B) antibodies
- Anti-Smith (anti-Sm) antibodies
- Anti-ribonucleoprotein (RNP)
- Antiphospholipid (aPL) antibodies including lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein 1 (anti-β2GP1)
- Anti-ribosomal P
- Anti-histone
- Anti-chromatin

Autoantibodies in SLE can be present for 5 to 7 years before clinical manifestations develop.[33]

Some of these auto-antibodies may also be found in healthy individuals. A study by Tan et al.[35] published in 1997, reported that, in a group of healthy individuals between the ages of 20 and 60 years old, 31.7%

were ANA positive at a serum dilution of 1:40, 13.3% were positive at a serum dilution of 1:80, 5% were positive at 1:160, and 3% were positive at 1:320. The most common autoantibodies found in healthy individuals are ANA, anti-Ro, and anticardiolipin antibodies. Anti-dsDNA and anti-RNP antibodies are rare in people without SLE.

A study published in 2006 compared the presence of ANA, anti-dsDNA antibodies, and eight other lupusrelated autoantibodies including Ro (SSA), La (SSB), Sm, RNP, Jo-1, chromatin, SCL-70, and ribosomal-P in patients with SLE, patients with undifferentiated connective tissue diseases, and unaffected first-degree relatives of patients with SLE versus 3000 normal individuals.[36] There was a 27% prevalence of ANA positivity in asymptomatic people. At least one additional autoantibody was found in 1.7% of the normal individuals.

Some lupus antibodies may be important in disease course.[37] Ng et al.[38] reported that, among patients with elevated levels of anti-dsDNA antibodies and low disease activity, up to 80% would experience a flare within 5 years of the detection of the elevated antibodies. However, on the day of an SLE flare, on average, anti-dsDNA decreases in the serum.[39]

It is very important to differentiate idiopathic SLE from drug-induced lupus erythematosus (DILE). DILE is a clinical syndrome with features similar to some of those of SLE. It can develop following the use of more than 90 different drugs.[40-46] The cause DILE can be divided into three groups:

- **Drugs definitely associated with DILE—there is strong evidence that these drugs cause DILE:**
  - Hydralazine ○ Procainamide ○ Isoniazid ○ Methyldopa ○ Chlorpromazine ○ Quinidine ○ Minocycline
  - Anti-tumor necrosis factor (anti-TNF)-α agents such as etanercept, infliximab, adalimumab
- **Drugs that may or possibly can cause DILE:**
  - Sulfasalazine
  - Antiepileptics such as carbamazepine, diphenylhydantoin, ethosuximide, phenytoin, primidone, trimethadione, valproate, zonisamide
  - Statins such as lovastatin, simvastatin, fluvastatin, atorvastatin, pravastatin ○ Antihypertensives such as methyldopa, acebutolol, atenolol, labetalol, enalapril, minoxidil, pindolol, practolol, metoprolol, timolol, pindolol, propranolol
  - Fluorouracil agents ○ Penicillamine ○ Terbinafine
- **Drugs that have at least one case report of DILE in the literature or are suggested to cause DILE:**
  - Gold salts ○ Griseofulvin ○ Penicillin ○ Alpha Interferons ○ Streptomycin ○ Phenylbutazone
  - Tetracycline ○ Hydroxyurea
  - Estrogens and oral ○ Para-aminosalicylic acid contraceptives ○ Clobazam ○ Tamoxifen ○ Tocainide ○ Lithium ○ Bupropion ○ Captopril ○ Taxanes
  - Lisinopril ○ Cyclophosphamide ○ Clonidine ○ Doxorubicin

- Lithium carbonate ○ Anastrozole ○ Ciprofloxacin ○ Bortezomib ○ Rifampicin ○ IL-2
- Calcium channel blockers ○ Lamotrigine

The increased use of immunotherapy in oncology (immune checkpoint inhibitors) has resulted in an increased number of reports of immune-related adverse events with these drugs.[47-50] The use of checkpoint inhibitors (anti-PD-1, anti PD-L1, and anti-CTLA-4 monoclonal antibodies) is currently limited but expanding rapidly. Currently, the approved anti-PD-1 drugs include nivolumab (Opdivo®) and pemobrolizumab (Keytruda®). ipilimumab (Yervoy®) is an approved anti-CTA-4 monoclonal antibody, and atezolizumab (Tecentriq®), avelumab (Bavencio®), and durvalumab (Imfinzi®) are approved PD-L1 monoclonal antibodies. These drugs are used to treat a wide variety of cancers.

The most common adverse events associated with checkpoint inhibitors tend to be related to tissue-specific inflammation.[49] These include skin rashes, pruritus, vitiligo, vomiting, diarrhea, colitis, hepatitis and elevated liver enzymes, thyroiditis, hypothyroidism, decreased pituitary function, adrenal insufficiency, and pneumonitis. Dry mouth, oral candidiasis and Sjögren's syndrome have also been reported. Fadel et al.[50] reported a case of anti-CTLA-4 monoclonal antibody-induced lupus nephritis. In addition, arthralgias have been reported with checkpoint inhibitors.[51-53] When evaluating patients with cancer treated with checkpoint inhibitors presenting with symptoms of a possible rheumatic disorder, it is important to keep in mind that the drugs used to treat the cancer may be responsible for the new symptoms of an autoimmune disorder.

The risk of developing DILE varies from 20% per year for procainamide, 5% to 8% per year for hydralazine, to less than 1% per year for quinidine and much less than 1% per year for most other drugs.[54]

Separately from DILE, many patients with established lupus can have their manifestations exacerbated by medications. Lupus patients may flare upon exposure to sulfa[55] antibiotics and echinacea.[56]

There are several findings in the clinical history, physical examination, and laboratory data that help to differentiate the idiopathic form of SLE from DILE. A history of treatment with a 'suspected' drug for at least 1 month is a helpful indicator when there is a suspicion of DILE. While idiopathic SLE characteristically has a female predominance, DILE occurs equally in both men and women. Drug-induced lupus is more common in older persons, because exposure to drugs is higher in this group.[57] Patients with DILE frequently present with arthralgia, myalgia, serositis, fever, and cutaneous manifestations; while renal and central nervous system manifestations are rare. Elevated titers of ANA are found in both idiopathic SLE and DILE. Anti-histone antibodies are present in 75% of DILE patients; however, they are not pathognomonic of DILE, because they can also be present in idiopathic SLE patients. Anti-dsDNA is positive in less than 5% of patients with DILE. Anti-Sm is almost exclusively found in idiopathic SLE and rarely in DILE. Symptoms of DILE may resolve over days or weeks after the drug is discontinued; however, serologic abnormalities, especially anti-histone antibodies, may persist much longer.[58]

Quality of Life and Economic Ramifications

Patients with SLE have a diminished quality of life, even when compared to patients with other chronic diseases such as diabetes and hypertension.[59] In particular, chronic fatigue (unrelated to lupus activity) can occur and often has the characteristics of fibromyalgia.

The cost of caring for patients with SLE is a significant burden to the healthcare system. Annual direct costs in the US ranged from $2,214 to $16,875 in 2010 dollars, according to Meacock et al.[31] In addition, patients with SLE incur indirect costs as a result of decreased productivity at work, increased absenteeism from work, reduced hours, early retirement, and loss of employment. In 2010 dollars, these were estimated to range from $2239 to $35 540.[31]

In 2015, Garris et al.[60] published a study of the cost of care for patients with SLE in the Medicare population. The study group consisted of 6707 patients with SLE and 13 414 non-SLE patients. The SLE group had 2.4 times more doctor visits, 2.7 times more hospitalizations, 2.2 times more outpatient visits, and 2.1 times more emergency department visits than the non-SLE group. Overall, the SLE group's annual medical costs exceeded those of the non-SLE group by approximately $10,229 per patient. In this study, close to 50% of the SLE patients were receiving disability benefits, and almost 2% of new disability cases in Medicare were related to SLE.

Diagnosis/Classification

In 1997, the American College of Rheumatology (ACR) published a revision to the 1982 Classification Criteria for SLE, with eleven criteria (Table 1).[61] For patients to be classified as having SLE, they had to meet four or more of these criteria; individuals meeting one to three criteria were said to have incomplete SLE. Although the 1982 criteria have been used very successfully by rheumatologists, the 1997 revisions were not adequate, especially in light of advances in the understanding of SLE.[62]

Table 1. The 1997 update of the 1982 ACR revised criteria for the classification of SLE

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
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 two or more peripheral joints characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician, or evidence of pleural effusion OR Pericarditis—documented by ECG or rub, or evidence of pericardial effusion

Renal disorder	Persistent proteinuria greater than .5 grams per day, or greater than 3+ if quantitation is not performed OR Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements such as uremia, ketoacidosis, or electrolyte imbalance OR Psychosis—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance
Criteria	**Definition**
Hematologic disorder	Hemolytic anemia—with reticulocytosis OR Leukopenia—less than 4000/mm^3 total on two or more occasions OR Lymphopenia—less than 1500/mm^3 on two or more occasions OR Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	Positive LE cell preparation OR Anti-DNA: antibody to native DNA in abnormal titer OR Anti-Sm: presence of antibody to Smith nuclear antigen OR 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
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 "DILE" syndrome

ACR, American College of Rheumatology; ANA, antinuclear antibody; anti-Sm, anti-Smith; DILE, drug-induced lupus erythematosus; DNA, deoxyribonucleic acid; ECG, electrocardiogram; LE cell, lupus erythematosus cell (usually a neutrophil or macrophage that has phagocytized, damaged nuclear material from another cell); SLE, systemic lupus erythematosus

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) published an evidence-based set of classification criteria for SLE (Table 2).[63] Classification criteria are not diagnostic criteria but are intended to be used to classify patients for clinical trials. Despite the initial intent they are used by many physicians as if they were diagnostic criteria. These criteria require that a patient have 4 or more of the listed criteria to be classified as having SLE. In addition, this classification system requires that the

patient must have at least one positive clinical and one positive immunologic finding. If lupus nephritis was confirmed by renal biopsy (with ANA or anti-dsDNA) that would be sufficient for classification.

Table 2. SLICC clinical and immunologic classification criteria for systemic lupus

Classification Criteria*

Acute Cutaneous Lupus
• Including lupus malar rash (do not count if malar discoid)
  ○ Bullous lupus
  ○ Toxic epidermal necrolysis variant of SLE
  ○ Maculopapular lupus rash
  ○ Photosensitive lupus rash (in the absence of dermatomyositis) ○ Subacute cutaneous lupus
  (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias)

Chronic Cutaneous Lupus • Including classical discoid rash ○ Localized (above the neck)   ○ Generalized (above and below the neck) • Hypertrophic (verrucous lupus) • Lupus panniculitis (profundus) • Mucosal lupus • Lupus erythematosus tumidus • Chilblains lupus • Discoid lupus/lichen planus overlap
Oral and Nasal Ulcers (in the absence of other etiologies such as vasculitis, inflammatory bowel disease, reactive arthritis, Behçet's disease, infection such as herpes, and acidic foods) • Palate • Buccal mucosa • Tongue • Nose
Nonscarring Alopecia (in the absence of other causes of alopecia such as alopecia areata, drugs, iron deficiency, and androgenic alopecia) • Diffuse thinning or hair fragility with visible broken hairs
Synovitis Involving 2 or more joints with swelling or effusion • Tenderness of two or more joints and at least 30 minutes of morning stiffness

Classification Criteria*
Serositis • Pleurisy for more than one day ○ Pleural fluid ○ Pleural rub • Pericardial pain (pain on lying down that gets better on sitting forward) for more than 1 day (in the absence of other etiologies such as infection, uremia, and Dressler's syndrome) ○ Pericardial effusion ○ Pericardial rub ○ Pericarditis on ECG
Renal • Urine protein/creatinine or 24-hour urine protein with 500 mg of protein/24 hours • Red blood cell casts
Neurologic • Seizures • Psychosis • Myelitis • Mononeuritis multiplex (in the absence of other known causes such as primary vasculitis) • Peripheral or cranial neuropathy (in the absence of other causes such as primary vasculitis, infection, and diabetes mellitus) • Acute confusional state (in the absence of other causes such as toxic-metabolic, uremia, or drugs)
Hemolytic Anemia
Leukopenia ○ <4000/mm^3 at least once in the absence of other causes such as Felty's syndrome, drugs, or portal hypertension **and/or** **Lymphopenia** ○ <1000/mm^3 at least once in the absence of other causes such as steroids, drugs, or infection
Thrombocytopenia ○ <100,000/mm^3 at least once in the absence of any other known cause such as drugs, portal hypertension, or TTP
Immunologic Criteria*
ANA • Above laboratory reference level
Anti-dsDNA • Above laboratory reference range, except with ELISA: twice above laboratory reference range

Classification Criteria*
Anti-Sm • Positive
Antiphospholipid antibody any of the following: • Lupus anticoagulant • False-positive RPR • Medium or high titer anticardiolipin (IgA, IgG, or IgM) • Anti-β2 glycoprotein I (IgA, IgG, or IgM)
Low complement • Low C3 • Low C4 • Low CH50
Direct Coombs test • Positive in the absence of hemolytic anemia

*The criteria are cumulative and thus need not all be present concurrently.

ANA, anti-nuclear antibodies; anti-dsDNA, anti-double stranded DNA antibodies; anti-Sm, anti-Smith antibody; C3, complement component 3; C4, complement component 4; CH50, hemolytic complement 50; dsDNA, double stranded deoxyribonucleic acid; ECG, electrocardiogram; IgA, interleukin A; IgG, interleukin G; IgM, interleukin M; RPR, rapid plasma reagin; SLICC, Systemic Lupus International Collaborating Clinics; TTP, thrombotic thrombocytopenia purpura

There is now a proposed third set of classification criteria by the European League Against Rheumatism (EULAR)/ACR (Table 3), developed for only clinical research.[64] These criteria include an entry criterion, a positive ANA of equal to or greater than 80. If that is met, the criteria are weighted, with a score of 10 required for classification.

Table 3. EULAR/ACR research classification criteria for systemic lupus

Clinical Domains and Criteria	Weight	Immunologic Domain and Criteria	Weight
Constitutional domain		*Antiphospholipid antibodies domain*	
Fever >38.3°C	2	Anticardiolipin IgG >40 GPL units or anti-β2GP1 IgG >40 units or lupus anticoagulant positive	2
Cutaneous domain			
Non-scarring alopecia	2		
Oral ulcers	2	*Complement proteins domain*	
Subacute cutaneous or discoid lupus	4	Low C3 or low C4	3

Acute cutaneous lupus	6	Low C3 and low C4 at the same time	4
Clinical Domains and Criteria	**Weight**	**Immunologic Domain and Criteria**	**Weight**
Arthritis domain			
Synovitis in ≥2 joints or tenderness in ≥2 joints and ≥30 minutes of morning stiffness	6		
Neurologic domain		*Highly specific antibodies domain*	
Delirium	2	Anti-dsDNA antibody	6
Psychosis	3	Anti-Smith antibody	6
Seizure	5		
Serositis domain			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic domain			
Leukopenia (<4000/mm^3)	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal domain			
Proteinuria >.5 g/24h	4		
Renal biopsy with Class II or V lupus nephritis	8		
Renal biopsy with Class III or IV lupus nephritis	10		
Classify as SLE if total score ≥10 points			

Anti-β2GP1, anti-β2-glycoprotein 1; C3, complement component 3; C4, complement component 4; dsDNA, double-stranded deoxyribonucleic acid; GPL, G phospholipids; IgG, interleukin-G; SLE, systemic lupus erythematosus

There is a so called “preclinical” or asymptomatic stage of SLE that can be as long as 5 to 6 years. During this phase of the disease, patients produce autoantibodies (some of which are seen in other autoimmune diseases and in healthy individuals) and gradually (up to 5 to 6 years) develop clinical signs of SLE. [33, 34]

Initial Evaluation

The initial evaluation should include at least the following:

- Complete medical history, including a complete drug and smoking history

- Complete physical examination
- Vaccination history
- Complete blood count (CBC) with differential
- Urinalysis, including microscopy, and urine protein/creatinine ratio
- Erythrocyte sedimentation rate and/or C-reactive protein (CRP)
- Liver function tests (LFTs)
- Complete metabolic panel
- 25(OH) Vitamin D level
- Consider baseline bone mineral density (BMD), in particular if there has been past corticosteroid use or if corticosteroid use is contemplated at that visit or in the near future
- Tuberculosis testing if patient has an endemic area
  Note: Hydroxychloroquine can cause an indeterminate QuantiFERON test.
- Any patient to be started on hydroxychloroquine should have a baseline ophthalmologic examination

EULAR recommends the following autoantibody and complement tests at the initial evaluation:[65]

- ANA
- Anti-dsDNA
- Anti-Sm
- Anti-RNP
- Anti-SSA (Ro)
- Anti-SSB (La)
- C3
- C4
- Lupus anticoagulant, anticardiolipin, and anti-β2GP1, false-positive rapid plasma reagin (RPR)
- Direct Coombs test

Evaluation of patients with neurologic manifestations is complex. Patients with a history of seizures should have magnetic resonance imaging (MRI) of the brain and an electroencephalogram (EEG). Those presenting with cognitive impairment should have neuropsychological testing and evaluation by a cognitive psychologist. Lupus patients with myelopathy should have a contrast-enhanced MRI of the spine and a cerebrospinal fluid analysis. Optic neuritis should be evaluated with a complete eye examination to include at least fundoscopy and fluorangiography, MRI, and visual evoked potentials. Those with an acute confusional state require a lumbar puncture for cerebrospinal fluid evaluation, an MRI of the brain, and an EEG to exclude non-SLE causes of the confusion.[66]

The ACR recommends that all patients with evidence of active lupus nephritis have a renal biopsy (unless strongly contraindicated) to document and classify the glomerular disease.[67] Indications for renal biopsy proposed by the ACR and EULAR include rising creatinine without another explanation.[65, 67] EULAR recommends biopsy at 500 mg proteinuria on a 24-hour specimen or a random spot urine protein/creatinine ratio.[65]

At the initial evaluation, the physician should complete at least a Physician Global Assessment (that can include visual analog scales for active organs[68]) and can consider using any of the versions of the SLE

Disease Activity Index to establish a baseline for each patient. The relevant form is included in the Appendix, together with a scoring system for the evaluation of flares. Also included in the Appendix is the Physician Global Assessment, with a score of 0 indicating no disease activity; and scores of 1, 2, and 3 indicating mild, moderate, and severe disease activity, respectively, with severe being the most severe expression possible in SLE.

United Rheumatology believes that the Lupus Low Disease Activity State (see Appendix) is the best treat-to-target goal in SLE. It combines low disease activity (Physician Global Assessment [PGA] ≤1; SLE Disease Activity Index [SLEDAI] ≤4) with prednisone ≤7.5 mg daily. Achieving a Lupus Low Disease Activity State (LLDAS) at 50% or more of follow-up visits leads to a 50% reduction in organ damage.[69] A LLDAS is recommended as part of routine care for SLE patients. Failure to achieve LLDAS on the current medication regimen would be an impetus to change the regimen, or to check on patient adherence.

Immunizations

Infection is one of the most common causes of morbidity and mortality in patients with SLE worldwide.[70-72] The disturbance of the innate and adaptive immunity, low complement levels, splenic dysfunction, and the use of steroids and immunosuppressive medications used to treat these patients increases their susceptibility to both classic and opportunistic infections.[72-75]

There is concern that some patients with SLE may have a potentially increased risk of disease activity with immunization.[76-79] However, two blinded trials of influenza and pneumococcal vaccine showed no increase in disease activity following vaccination.[80, 81] The possibility of live attenuated vaccines inducing active infection remains a real concern and argues against the use of live viral vaccination in severely immunocompromised SLE patients.[70]

The EULAR recommendations for vaccination in patients with autoimmune inflammatory rheumatic disease were published in 2010.[82] The association cautions that these recommendations are based on limited data and additional studies are needed. However, at this time, EULAR acknowledges that there are vaccine-preventable diseases that occur in patients with autoimmune diseases and that most vaccines are effective in patients with SLE, even when they are taking immunosuppressive drugs, with the exception of rituximab.

Streptococcus pneumoniae accounts for about 6% to 18% of bacterial infections in SLE patients.[83] Pneumococcal vaccine is recommended for SLE patients,[84, 85] first, with pneumococcal 13 (a one-time vaccine). The "booster" pneumococcal vaccine, a 23-valent polysaccharide vaccine which contains capsular polysaccharides antigens from the 23 most dominant serotypes of *S. pneumoniae* responsible for approximately 90% of the invasive infections in adults, can be given 8 weeks up to 1 year later, followed by at least 5 years for two more doses.[84] The Centers for Disease Control and Prevention (CDC) recommends three boosters over a lifetime.[86] For an SLE patient, that would mean 0, 5, and 10 years. As patients with SLE are often young, current CDC guidance is unclear what to do after that. Infectious disease consultant Kevin Winthrop MD MPH, provided his opinion that there will be additional updates on pneumococcal vaccine guidelines over the next 10 years (personal communication).

Some studies have shown that immunosuppressive treatment did not affect the response to pneumococcal vaccine,[87, 88] while others demonstrated that it might decrease the response.[89, 90] Consequently, it is better to give the pneumococcal vaccination before the initiation of

immunosuppressive therapy, whenever possible. Revaccination every 5 years is advisable to maintain an adequate antibody response post vaccination.[73]

The EULAR guidelines also recommend that patients with SLE receive annual influenza vaccinations.[82]

In addition, the EULAR guidelines indicate that consideration should be given to human papillomavirus (HPV) vaccination in patients with SLE. A case-controlled study of 50 lupus patients and 50 healthy controls evaluated the efficacy and safety of the HPV vaccine.[91] The results of this study showed an adequate response in most SLE patients; however, patients treated with mycophenolate mofetil and steroids had a lower response to the vaccine.

Hepatitis B (HBV) vaccine is the recombinant deoxynucleic acid (DNA) of hepatitis B surface antigen. It has been reported to be a potential trigger for autoimmune diseases such as vasculitis,[92-96] transverse myelitis,[97] uveitis,[98] immune thrombocytopenia,[99-102] RA,[92, 103, 104] spondyloarthropathies,[92] and SLE.[92, 104, 105] A prospective study evaluated the safety and efficacy of HBV vaccine in 28 inactive SLE patients for 7 months.[105] The authors found no significant change from baseline in the frequency of exacerbations, the SLEDAI score, anti-DNA antibodies, steroid dose, or the use of immunosuppressive drugs. They also reported adequate seroconversion at the end of the study (93%), although it was lower than the controls after the first and the second doses (58%). EULAR recommends the use of HBV vaccine for inactive, highrisk SLE patients such as healthcare providers and those in contact with infected individuals.[82]

The new herpes zoster vaccine is inactivated and more effective than the previous live attenuated vaccine.[106] There are no studies yet in SLE. However, as zoster is frequent in SLE, there is a clear need for effective zoster prevention.

Treatment

Prevention and treatment of flares to minimize organ damage are the goals of therapy in SLE. The treatments are highly variable and individualized; they are developed according to the needs of each individual patient. In particular, treatment is based on the organ system involvement, and within each organ, on the severity of the lupus activity.

Treatment for SLE varies depending on the clinical presentation and severity of disease. The drugs used for the treatment of SLE have been associated with a number of potentially serious adverse effects. Physicians should be familiar with the Food and Drug Administration (FDA)-approved package inserts for the medications discussed below and with the management of potential complications and drug interactions.

The pharmacologic treatment of SLE has slowly evolved and now includes several classes of drugs:

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids
- Immunomodulating drugs
    - Antimalarials (hydroxychloroquine, quinacrine, chloroquine)
    - Dehydroepiandrosterone (DHEA)
    - Vitamin D

- Immunosuppressive drugs ○ Methotrexate ○ Leflunomide ○ Azathioprine ○ Cyclophosphamide ○ Mycophenolate mofetil
- Calcineurin inhibitors (CNIs) ○ Tacrolimus
  ○ Cyclosporine (rarely used)
- Biologics ○ Rituximab ○ Belimumab
  ○ Some biologics approved for RA, including, but not limited to, abatacept, tocilizumab, and tofacitinib may occasionally be used in SLE. Anti-TNF is generally not used (except in patients who have true RA *and* SLE (rhupus)).

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs may be used to help control pain, swelling, and fever. However, doses should be adjusted, as appropriate, for the overall health of the patient, any existing comorbidities, and potential drug interactions. Patients with lupus nephritis should not chronically take NSAIDs. Chronic use of NSAIDs increases the risk of cardiovascular disease. Ibuprofen can cause aseptic meningitis in SLE.[107]

Corticosteroids

Corticosteroids remain the fastest onset and most broadly effective immunosuppressants in the treatment of SLE. Unfortunately, they also are directly or indirectly responsible for 80% of the permanent organ damage by 15 years after diagnosis.[108] Corticosteroids predispose to immediate (psychosis, insomnia, depression, hyperlipidemia, hyperglycemia, hypertension) and long-term (osteoporosis, osteonecrosis, cardiovascular disease, cataracts, diabetes, obesity) sequelae.

For acute organ threatening or life-threatening events, SLE pulse methylprednisolone 1000 mg daily for 3 days (given over 90 minutes) is useful. It can be followed by the lowest appropriate oral prednisone dose AND addition of appropriate immunosuppression.

For mild/moderate lupus flares, an oral Medrol dose pack or triamcinolone 100 mg IM can be used. Both are effective for the majority of flares and avoid the need for any increase in maintenance oral prednisone.[109]

Any oral prednisone dose of 6 mg or higher increases permanent organ damage by 50% (Table 4).[110]

Table 4. Effect of prednisone on organ damage adjusting for confounding by indication due to SLE disease activity

Prednisone Average Dose	Hazard Ratio
> 0-6 mg/day	1.16
> 6-12 mg/day	1.50
>12-18 mg/day	1.64

>18 mg/day	2.51

SLE, systemic lupus erythematosus

Any oral maintenance dose of 10 mg increases cardiovascular events 2.4-fold; 20 mg increase the risk of cardiovascular events 5-fold (Table 5).[111]

Table 5. Prednisone by itself increases the risk of cardiovascular events

Prednisone Use	Observed Number of CVE	Rate of Events per 1000 Person Years	Age-adjusted Rate ratios (95% CI)	*P* value
Never taken	22	13.3	1.0 (reference group)	
Currently taking				
1-9 mg/day	32	12.3	1.3 (.8, 2.0)	.31
10-19 mg/day	**31**	**20.2**	**2.4 (1.5, 3.8)**	**.0002**
≥20 mg/day	**25**	**35.4**	**5.1 (3.1, 8.4)**	**<.0001**
Cumulative past dose				
<3650 mg	14	9.9	.9 (.4, 1.6)	.56
3650-10,950 mg	26	13.8	1.2 (.7, 2.2)	.49
10,950-36,499 mg	41	12.8	1.1 (.6, 1.8)	.83
≥36,500 mg	**30**	**25.3**	**2.2 (1.2, 3.7)**	.0066

CI, confidence interval; CVE, cardiovascular events

Immunomodulating Drugs

Hydroxychloroquine

Initially all SLE patients should be started on hydroxychloroquine, unless contraindicated.[112-114] It is not necessary to check G6PD before starting.[109] Other antimalarials include quinacrine and chloroquine.

Hydroxychloroquine immunomodulatory effects in SLE include many different molecular pathways.[115-119] As a weak base, it increases the lysosomal pH in antigen presenting cells, which interferes with phagocytosis and disrupts self-antigen presentation.[120, 121] It also alters T-cell responses and inhibits numerous cytokines (IL-1, IL-2, IL-6, IL-17, IL-22, interferon [IFN]-α, and TNF-α).[115-119] Its Immunomodulatory action, in particular, may be exerted through the inhibition of Toll-like receptor activation.[122] Hydroxychloroquine decreases signaling of Toll-like receptors 3, 7, 8, and 9; which decreases dendritic-cell activation and IFN production,[106] among other mechanisms.[123]

For most patients, the initial dose of hydroxychloroquine has classically been ≤6.5 mg/kg/day, not to exceed 400 mg/day. Recent US ophthalmology guidelines have suggested ≤5.0 mg/kg/day.[124] In patients with renal insufficiency, the dose is decreased to 200 mg/day; and for those on dialysis, the dose is 200 mg three times per week. Adherence can be monitored by blood (not plasma) levels. In some studies, as many as 50% of patients are nonadherent.[125]

Contraindications to the use of hydroxychloroquine include known allergy to the drug, to 4-aminoquinoline derivatives, or to any component of the drug. Another contraindication is the development of hydroxychloroquine retinopathy.[114] Current guidelines recommend one or more of the newer retina monitoring tests such as ocular coherence tomogram along with visual fields.[124] Screening should be done within the first year, and annual screening after 5 years of use. As many SLE patients did not have a pretreatment baseline, a retina expert must interpret abnormal tests. In the past, hydroxychloroquine was thought to be contraindicated in patients with myasthenia gravis,[126] but recent data from a study of 17 patients with both SLE and myasthenia gravis who were treated with hydroxychloroquine found that hydroxychloroquine was safe in these patients.[127] Some patients develop hyperpigmentation; very rare toxicities of hydroxychloroquine include cardiomyopathy and myopathy.

Hydroxychloroquine has many benefits in the management of patients with SLE, including

- **Decreased (by 50%) SLE activity and reduced lupus flares**.[112] A Canadian report found that withdrawal of hydroxychloroquine increased the risk of a flare 2.5 times.[128] Another report indicated that hydroxychloroquine did not reduce severe flares.[129]

- **Effective management of skin disease and arthritis**. In fact, hydroxychloroquine is considered the first drug of choice for patients with skin involvement.[130-133]

- **Protection against thrombosis**,[134-136] including patients with positive aPL antibodies.[137-140]

- **Anti-diabetic effect**. Many patients with diabetes and SLE treated with hydroxychloroquine show improved blood glucose levels.[141, 142]

- **Lipid-lowering effect**.[143-145]

- **Independent predictor of complete renal remission in patients with lupus nephritis treated with mycophenolate mofetil**. The remission rate was three times higher in those treated with hydroxychloroquine and mycophenolate mofetil when compared to those treated with mycophenolate mofetil alone.[146]

- **Improvement of pregnancy outcomes**.[147-149] A reduction in pre-eclampsia has been found.

- **Reduced risk of congenital heart block in neonates born to mothers with positive Ro (SSA) antibodies**.[150]

- **Increase in survival**.[138, 151, 152] In a case-control study performed within the context of a multiethnic US cohort (LUMINA), in which deceased patients were matched for disease duration (within 6 months) with living patients (controls) in a proportion of 3:1 investigators found that hydroxychloroquine had a protective effect on survival.[151] Similar results were shown with the Multinational Latin American Inception Cohort (GLADEL) study.[152] A recent study from China confirmed the survival benefit.[153]

- **Delayed onset of SLE in those with undifferentiated connective tissue disease**.[154]

Under certain circumstances, chloroquine (for severe skin disease) or quinacrine can be substituted for hydroxychloroquine. Quinacrine can be added to hydroxychloroquine for severe cutaneous lupus.

Dihydroepiandrosterone

Dihydroepiandrosterone (DHEA) is the major product of the normal adrenal glands. In women with SLE, levels may be low. In premenopausal women, replacement with 200 mg was shown to be beneficial in two randomized clinical trials[155, 156] as well as beneficial for BMD.[157] It should not be given to men (due to reduction in endogenous testosterone) or to post-menopausal women (due to an increase in estrogen level). It is not FDA-approved for the treatment for SLE.

Vitamin D

Vitamin D deficiency is common among patients with SLE. Therefore, it is important to maintain a vitamin D level of 40 ng/mL in these patients.[158, 159]

The cause of the deficiency is multifactorial and includes avoidance of sun exposure; use of sunscreen; renal insufficiency; and medications such as steroids, antimalarials, and antiepileptic drugs.[160-165]

Cross-sectional cohort studies from all over the world have demonstrated an association between low levels of vitamin D in patients with SLE and higher disease activity using scoring measures such as SLEDAI, British Isles Lupus Assessment (BILAG), and the European Consensus of Lupus Activity Measurement (ECLAM).[166] A cohort study of 181 women with SLE evaluated the associations of serum vitamin D levels with cardiovascular risk in this patient pool.[167] The study suggested an association between lower vitamin D levels and higher body mass index (BMI), diastolic blood pressure, LDL cholesterol, and diabetes in female SLE patients.

Mok et al.[168] studied 290 patients with SLE and found that low levels of vitamin D were associated with higher atherogenic lipoprotein indices (total/high-density lipoprotein [HDL] cholesterol ratio).

Another cohort study of 75 female SLE patients demonstrated that vitamin D deficiency was associated with increased vascular stiffness in SLE, independent of traditional cardiovascular risk factors and insulin resistance. These investigators reported no association between vitamin D and carotid plaque.[169] However, Ravenell et al.[170] demonstrated a significant association between vitamin D level and total carotid plaque area in African American patients with SLE.

In the largest prospective cohort study, 1006 patients with SLE, who presented with initial vitamin D levels below 40 ng/mL were supplemented with 50 000 IU vitamin D2 weekly and followed for 128 weeks.[159] Higher levels of vitamin D were associated with statistically significant improvement in the urine protein to creatinine ratio. There was also a statistically significant relationship between the change in serum 25(OH) vitamin D and global SLE clinical disease activity measured by the Physician Global Assessment.[159]

A controlled trial, in which 267 lupus patients were randomized 2:1 to receive either oral vitamin D at 2000 IU/day or placebo for 12 months, showed a significant improvement in levels of inflammatory and hemostatic markers and in disease activity in the treatment group compared to the placebo group.[171] In accordance with these results, Lima et al.,[172] in a 24-week randomized, double-blind, placebo-controlled trial including 60 juvenile-onset SLE patients; found that vitamin D supplementation was associated with a decrease in disease activity and improvement of fatigue in these patients.

In a randomized controlled study, Swan et al.[173] evaluated the relationship of vitamin D supplementation and BMD increase in premenopausal patients with SLE taking both corticosteroids and bone-active medication. They demonstrated that patients with higher vitamin D levels had a better BMD response during treatment with bone-active agents and advised vitamin D supplementation until a vitamin D level of at least 30 ng/mL was reached.

The benefits of vitamin D supplementation in patients with SLE include at least the following:

- Reduced disease activity,[159, 171, 172] especially proteinuria
- Reduced cardiovascular risk[168]
- Improved bone health[173]

Immunosuppressive Therapy

Methotrexate

Methotrexate is the most commonly used disease-modifying antirheumatic drug (DMARD) for the treatment of RA.[174] In 2014, Sakthiswary and Suresh[175] published a systematic review of methotrexate in patients with SLE and found that methotrexate effectively reduced disease activity based on the SLEDAI scale and decreased corticosteroid use.

Other studies have shown that methotrexate is most effective in the management of SLE patients with articular and cutaneous manifestations.[176-180] There is no evidence from randomized controlled trials that methotrexate is beneficial in other organ manifestations of SLE. A small controlled study of 30 SLE patients, 12 of whom had lupus nephritis, found that, after treatment with methotrexate, serum protein decreased in 4 of the participants, remained unchanged in 4 and increased in 4 patients.[181]

Methotrexate is used in doses ranging from 7.5 to 25 mg/week orally, but should be used subcutaneously if the dose is greater than 15 mg weekly. This drug can take up to 3 months to demonstrate its effectiveness, although patients may improve as quickly as 3 to 6 weeks. Daily folate supplements are required to decrease some of the side effects of this medication; which include nausea, vomiting, stomatitis, and elevated LFTs.[182] Methotrexate can never be used in pregnancy or renal failure.

Leflunomide (Arava®)

Leflunomide is a DMARD sometimes used in RA when patients fail to respond to methotrexate. This drug works by inhibiting the synthesis of RNA and DNA in both T and B lymphocytes by blocking the *de novo* pyrimidine synthesis pathway.

It may take up to 12 weeks to see improvement in disease activity with leflunomide. The most common side effect of leflunomide is diarrhea, which usually is self-limited. Other side effects are nausea, headache, rash, dyspepsia, alopecia, and infection. Elevated LFTs can occur and should be routinely monitored. According to the Arava package insert, LFTs should be monitored at least monthly for 6 months after starting leflunomide and every 6 to 8 weeks thereafter.[183] It should not be used in pregnancy.

Leflunomide has been reported to have a 30% response rate in SLE patients with refractory synovitis when given at high doses of 40 mg for at least 3 months.[184]

This drug has also been evaluated for the management of lupus nephritis. Wang et al.[185] reported on the results of a small observational prospective study with 110 patients with biopsy-proven lupus nephritis. Seventy patients were treated with leflunomide and 40 with cyclophosphamide. Both groups were given prednisone. The leflunomide group showed complete remission in 21% and partial remission in 52% of patients; in the cyclophosphamide group 18% of patients showed complete and 55% partial remission. Renal function tests and disease activity scores improved in both groups.

A systematic review and meta-analysis including 254 patients with lupus nephritis evaluated the efficacy and safety of leflunomide versus cyclophosphamide for the treatment of lupus nephritis.[186] Leflunomide was found to be more effective than cyclophosphamide for improving renal function and achieving complete remission. It appeared to be equal to cyclophosphamide in improvement of disease activity and serum albumin. Leflunomide had a somewhat safer profile than cyclophosphamide with respect to hepatoxicity and infection. In 2010, leflunomide was approved in doses up to 40 mg a day in China for lupus nephritis. Although not FDA approved for SLE, it could be considered, especially in a patient with both nephritis and arthritis.

Azathioprine (Imuran®)

Azathioprine is a DMARD usually taken orally, but may also be given intravenously. It is an immunosuppressant drug that is used for lupus nephritis, cutaneous lupus and hematological manifestations of SLE. It is considered to be a steroid-sparing agent.[67, 187-190]

Azathioprine is not itself an active drug. It must be converted to its active components, 6-mercaptopurine and 9-thioinosince acid, in the body by intracellular metabolism. In its active form, azathioprine interferes with DNA synthesis in dividing cells.

It has been used successfully for long-term maintenance of patients with lupus nephritis.[191-193] It has also been shown to decrease nephrotic syndrome and recurrences.[192]

Thiopurine methyltransferase genetic testing is recommended before starting azathioprine to identify “slow metabolizers” at greater risk for toxicity.

The most common side effects of azathioprine include nausea, vomiting, abdominal pain, and diarrhea. Hepatitis and pancreatitis have also been reported. There are drug interactions with allopurinol, warfarin, sulfasalazine, olsalazine, and mesalamine. Azathioprine has been associated with leukopenia and pancytopenia. Long-term use has been associated with an increased risk of cancer.[194]

Azathioprine has a slow onset of action of up to 6 to 12 weeks. During the first month of treatment a CBC should be performed one week after starting, with periodic monitoring thereafter.[194]

The Imuran package insert cautions that azathioprine should not be used in pregnant or nursing women.[194] However, several studies demonstrated that it may safely be used during pregnancy and lactation.[194-200]

This drug is used in SLE patients without lupus nephritis to control disease activity and prevent flares. In some cases, the prednisone dose can be decreased.[192]

The ACR recommends azathioprine, among other drugs, for maintenance therapy but not for induction in patients with lupus nephritis, at a recommended dose of 2 mg/kg/day plus low-dose glucocorticoids.[67] According to the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) guidelines,[187] azathioprine may be used for both

induction and maintenance. It is used as an alternative to mycophenolate mofetil for induction if mycophenolate is contraindicated. The recommended dose of azathioprine is 2 mg/kg/day for induction. The maintenance dose should be continued for at least 3 years. If drug withdrawal is considered, prednisone should be tapered first.[187]

Cyclophosphamide (Cytoxan®)

This is a potent immunosuppressive drug and is considered to be mostly a rescue drug for severe organ threatening SLE.[201] Cyclophosphamide is an alkylating agent that is metabolized in the liver to its active form. The metabolites prevent replication of actively dividing cells by interfering with DNA replication. Side effects of cyclophosphamide include[202]

- Leukopenia
- Thrombocytopenia
- Loss of appetite
- Infection
- Gonadal failure
- Abdominal pain or discomfort
- Alopecia
- Hemorrhagic cystitis and urinary bladder fibrosis
- Malignancy

Cyclophosphamide is excreted in breast milk and should not be used during lactation.[203] It is also considered to be teratogenic and should be stopped before pregnancy.[200]

In patients with SLE, cyclophosphamide is usually administered in an intermittent intravenous (IV) schedule. The efficacy of this approach was demonstrated by trials performed at the National Institutes of Health (NIH).[204, 205] There are two regimens for IV cyclophosphamide. The high dose (NIH regimen) has been used for lupus nephritis and consists of .75 to 1.0 g/m^2 IV cyclophosphamide given monthly for 6 months and then quarterly for up to 2 more years. The low-dose IV regimens (Euro-Lupus regimen) consists of six doses of 500 mg every 2 weeks. The 10-year follow-up of the Euro-Lupus Nephritis Trial showed both cyclophosphamide regimens to have similar results.[206]

Intravenous cyclophosphamide, in combination with glucocorticoids, is still recommended by both the EULAR/ERA-EDTA and ACR for the induction of remission of proliferative lupus nephritis, although in practice, mycophenolate mofetil is usually used.[67, 187]

Cyclophosphamide is also an important treatment option for severe neuropsychiatric lupus. The efficacy of cyclophosphamide in neuropsychiatric lupus has been demonstrated in a number of case series,[207-209] cohort studies,[210-213] and one small randomized controlled trial involving 32 patients with SLE and neuropsychiatric manifestations.[214] In this latter study, patients were randomized into two groups. After induction therapy, patients in the first group were treated with IV cyclophosphamide monthly, those in the second group with IV methylprednisolone bimonthly every 4 months for 1 year and then IV cyclophosphamide or IV methylprednisolone every 3 months for another year. One patient in the cyclophosphamide-only group failed to improve versus seven patients in the methylprednisolone group. Cyclophosphamide was significantly more effective than methylprednisolone in patients with seizures,

peripheral neuropathy, optic neuritis, and brainstem disease; while differences were not clear in coma and myelitis.[214]

Cyclophosphamide has also been used for the treatment of diffuse alveolar hemorrhage, which can be a severe life-threatening complication of SLE. Data show conflicting results. Zamora et al.[215] reported that the use of cyclophosphamide was associated with higher mortality than that seen in patients not treated with cyclophosphamide. Martinez et al.[216] demonstrated a potential benefit of cyclophosphamide in patients with SLE and diffuse alveolar hemorrhage, although the results were not statistically significant.

Cyclophosphamide has been used in SLE patients who develop catastrophic antiphospholipid syndrome (CAPS).[217, 218] The multivariate analysis data of the CAPS Registry showed that cyclophosphamide decreased mortality rates in patients with SLE associated with CAPS.[218] However, rituximab or eculizumab may be better current options.[219, 220]

Mycophenolate Mofetil

Mycophenolate mofetil is an immunosuppressive agent widely used to prevent acute rejection in solid organ transplantation. More recently, it is increasingly used in the treatment of patients with lupus nephritis, where it has been shown to be effective as both induction and maintenance therapy.[221, 178]

Mycophenolate mofetil is a selective inhibitor of inosine monophosphate dehydrogenase that catalyzes the *de novo* synthesis of purine nucleotides. It inhibits T and B cell proliferation and autoantibody production, inducing activated T cell apoptosis, downregulation of adhesion molecule expression, and inhibition of dendritic-cell maturation.[222]

Potential side effects of this drug include infection, nausea, vomiting, diarrhea, cytopenias, nonHodgkin's lymphoma, and all malignancies.[223-225] Mycophenolic acid can be used instead of mycophenolate mofetil, if there are gastrointestinal (GI) side effects, although a clinical trial showed mycophenolic acid might have fewer side effects.[226].

The efficacy of mycophenolate mofetil in the treatment of lupus nephritis is well established by multiple randomized controlled trials[223, 225, 227, 228] and a number of meta-analyses.[202, 229, 230] Furthermore, mycophenolate mofetil is recommended by the EULAR/ERA-EDTA as the first choice in lupus nephritis Classes III and IV and an equivalent choice in Class V.[187] The ACR considers mycophenolate mofetil equivalent to cyclophosphamide in lupus nephritis Class III/IV (Level A) and pure membranous lupus nephritis (Class V).[67]

The efficacy and safety of mycophenolate mofetil in the treatment of nonrenal manifestations of SLE have been evaluated in cohort studies and small case series.[224, 231-237] The Aspreva Lupus Management Study (ALMS) evaluated the efficacy and safety of mycophenolate mofetil in nonrenal manifestations as a secondary end point and indicated that mycophenolate mofetil showed similar efficacy in treating nonrenal manifestations; particularly mucocutaneous, musculoskeletal, and hematologic features.[238] Another double-blind, placebo-controlled trial showed that although it is not the best choice, mycophenolate mofetil has some benefit in the treatment of patients with SLE and arthritis.[223] A recent retrospective observational cohort study evaluated the efficacy of mycophenolate mofetil in patients with extrarenal manifestations of SLE. The study followed 177 patients with SLE (72 with extrarenal manifestations) for 12 months. The authors reported some benefit of mycophenolate mofetil in musculoskeletal, cutaneous, neuropsychiatric, serological, and hematological lupus manifestations, as well as a significant corticosteroid-sparing effect.[239]

Mycophenolate mofetil is used as induction therapy in the treatment of lupus nephritis. The ACR guidelines recommend a dose of 2 to 3 g/day for 6 months plus glucocorticoids, followed by maintenance with mycophenolate mofetil for 3 years.[67] If mycophenolate mofetil is used for induction, the European guidelines suggest a dose 3 g/day for 6 months, followed by maintenance therapy at a dose of 2 g/day for at least 3 years.[187] Asian women may need lower doses of 1,000 mg twice daily for induction. Mycophenolate is forbidden in pregnancy. The FDA has a REMS program for patients. In addition to teratogenicity, it interferes with oral contraceptive efficacy.

Calcineurin Inhibitors—Tacrolimus

Calcineurin inhibitors are immunosuppressant drugs that inhibit the activation of T cells by interfering with the action of calcineurin (a protein phosphatase needed for the activation of T cells). Both cyclosporine and tacrolimus are CNIs commonly used to prevent rejection of solid organ transplants, especially renal transplants.[240, 241] Tacrolimus is the CNI used most often. Topical pimecrolimus and tacrolimus are useful for cutaneous lupus.[242]

Both drugs act through reduction of IL-2 transcription and inhibition of T cells[243] and have been shown to decrease the production of IL-2, IL-4, IL-5, IFN-γ, and TNF.[244] However, tacrolimus is 10- to 100-fold more potent than cyclosporine.[244]

The efficacy of tacrolimus in lupus nephritis has been demonstrated in cohort studies,[245-247] randomized controlled trials,[248-254] and meta-analyses.[255, 256] The efficacy of cyclosporine in lupus nephritis has been demonstrated in uncontrolled studies,[257, 258] randomized controlled studies,[259-261] and meta-analyses.[255, 256]

One meta-analysis compared CNIs to cyclophosphamide for the induction therapy of active lupus nephritis.[255] The report included six controlled trials (with a total of 265 patients), four of which compared tacrolimus with cyclophosphamide and two others that compared cyclosporine to cyclophosphamide. The authors found that CNIs resulted in higher complete remission rates, better total remission rates, and fewer side-effects than cyclophosphamide. Tacrolimus demonstrated more favorable results than cyclosporine. A subsequent meta-analysis of 65 randomized controlled trials, reported no difference in the renal outcome between azathioprine, cyclophosphamide, tacrolimus, and mycophenolate mofetil.[256] More recently, a meta-analysis of 12 randomized controlled trials and one cohort controlled trial with tacrolimus revealed that tacrolimus showed better complete and partial remission rates than cyclophosphamide during the induction phase in patients with active severe lupus nephritis.[262] Tacrolimus and mycophenolate mofetil resulted in similar remission rates. The combination therapy of mycophenolate mofetil and tacrolimus was superior to cyclophosphamide for achieving remission in patients with refractory lupus nephritis.[262]

An important advantage of CNIs is their safe use during pregnancy[263] and lactation.[200]

Adverse effects of tacrolimus were similar to other immunosuppressants used in the management of lupus nephritis. Tacrolimus was associated with fewer GI side effects, leukopenia, menstrual disorders, infections, and episodes of liver dysfunction, but with a greater incidence of new hypertension and hyperglycemia.[262]

Adverse reactions reported with tacrolimus include but are not limited to the following:[264]

- Increased incidence of malignancy, especially lymphomas

- Serious infections
- Diabetes
- Neurotoxicity
- Hyperkalemia
- Hypertension
- Myocardial hypertrophy
- Pure red cell aplasia
- Nephrotoxicity

Adverse reactions reported with cyclosporine include but are not limited to the following:[265]

- Hyperkalemia
- Thrombotic microangiopathy
- Hepatotoxicity
- Increased incidence of malignancy
- Neurotoxicity
- Hypertension
- Nephrotoxicity

Practically, tacrolimus is the preferred CNI in SLE. The starting dose is .5 mg twice daily with monthly increments depending on response. It is widely used in Asia.[266]

Biologics

Rituximab

Rituximab is an anti-CD20 monoclonal antibody leading to peripheral B cell depletion.[267, 268]

There are two double-blinded, randomized controlled studies evaluating the efficacy of rituximab in SLE. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial evaluated the efficacy and safety of rituximab in patients with moderately-to-severely active extrarenal SLE.[269] Investigators enrolled 257 SLE patients with either at least one organ system involved and a BILAG A score (severe disease activity) or at least two organ systems involved and a BILAG B score (moderate disease activity). Patients were randomized at a 2:1 ratio to receive either IV rituximab (1000 mg) or placebo on Days 1, 15, 168, and 182; in addition to prednisone and the baseline immunosuppressive regimen. There was no difference between the rituximab and placebo group (standard of care) after 1 year. However, a beneficial effect of rituximab was observed in the African American and Hispanic subgroups.[269]

The Lupus Nephritis Assessment with Rituximab (LUNAR) trial included 144 patients with new or relapsed biopsy-proven proliferative lupus nephritis.[270] Patients were randomized into a placebo or rituximab group. The rituximab group received 1000 mg of the drug intravenously on Days 1, 15,168, and 182. Both groups received 1000 mg methylprednisolone 30 to 60 minutes before either the placebo or rituximab on Day 1 and again within the next 3 days. In addition, all participants received oral prednisone and mycophenolate mofetil. This trial also failed to meet its primary end point, with no difference in the complete and partial remission rates between the groups after 1 year.[270]

On the other hand, a recent systematic review[271] including one randomized controlled trial[269], two openlabel studies,[272, 273] and 22 cohort studies,[274-295] with a total of 1231 patients, evaluated the efficacy

and safety of rituximab in the treatment of nonrenal SLE. Rituximab was found to be safe and effective for the treatment of patients with nonrenal SLE.[271]

There are no controlled trials evaluating the efficacy of rituximab in neuropsychiatric lupus. However, data from case series[277, 296, 297] and cohort studies[277, 290, 292, 294, 295] show promising results. Collected data of 34 patients with SLE and neuropsychiatric manifestations treated with rituximab demonstrated an overall response rate of 85%. After a median of 10 months, 45% of these patients relapsed, despite being on maintenance therapy.[297]

Adverse reactions associated with rituximab in the EXPLORER and LUMINA trials were mild and most frequently infusion-related reactions or upper respiratory tract infections. However, potential rituximab side-effects include infection (including progressive multifocal leukoencephalopathy), neutropenia, hypogammaglobulinemia, and infusion reactions.

Recently, rituximab has been used sequentially, followed by belimumab, in the SynBiose regimen. Long-term important efficacy was found, including lupus nephritis.[298] It has also been used with mycophenolate, but without any oral steroids, in the Rituxilup regimen.[299]

Belimumab

Belimumab is a fully humanized monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS or BAFF). B-lymphocyte stimulator is a key cytokine required for B-lymphocyte survival.[300-302] It is overexpressed in patients with SLE, and increased levels correlate with greater disease activity (based on the SELENA-SLEDAI scoring system) and predict flares.[303-305]

Belimumab is the only biologic approved by the US FDA and the European Medicines Agency for the treatment of patients with active seropositive SLE with low complement and positive anti-dsDNA antibodies. It is approved as an IV infusion at a dose of 10 mg/kg on Days 0, 14, and 28; and then every 28 days.[306] In 2017, it was approved as a weekly subcutaneous injection.[307]

The Phase III clinical trials for belimumab included BLISS-52[308] and BLISS-76.[309] Both trials were double-blind, placebo-controlled, multicenter investigations to evaluate the efficacy and safety of two doses of belimumab (1 and 10 mg/kg) plus standard of care versus placebo plus standard of care, in seropositive (ANA >1:80 and/or anti-dsDNA antibodies >30 IU/mL) patients with SLE and SELENA–SLEDAI scores of at least 6. The primary efficacy endpoint was defined as improvement in the Systemic Lupus Erythematosus Responder Index (SRI) at Week 52 (reduction of at least four points in the SELENA-SLEDAI score; no new BILAG, and no worsening in PGA score).[308, 309]

Pooled data from the two Phase III trials showed that belimumab led to significant sustained reductions of autoantibodies (anti-dsDNA, anti-Sm, anticardiolipin, and anti-ribosomal P autoantibodies) as well as reversal of hypocomplementemia.[310] Belimumab treatment also led to reductions in numbers of naïve and activated B cells and plasma cells while preserving the memory B cell subset and T cell populations.[310]

A *post hoc* analysis of the belimumab trials demonstrated that high disease activity, serological activity (low complement or high anti-dsDNA), and the need for prednisone identified patients likely to respond to this biologic.[311]

In an open-label continuation (to 7 years) of the Phase II study of belimumab aimed at assessing the efficacy and safety of belimumab plus standard therapy in patients with and mild or moderate disease activity.[312] There was sustained disease control and a decreased frequency of all (including severe) flares

throughout the study. The safety of belimumab, including infections, were generally stable or decreased during 7 years of treatment.[312]

The efficacy of belimumab in black/African American patients with SLE has been evaluated in a retrospective cohort study.[313] The study included 58 African American SLE patients—76% had high anti-dsDNA; 59% had low C3 or C4; and 2%, 71%, and 28% had mild, moderate and severe disease, respectively. After 6 months of belimumab therapy, most patients had improvements in clinical manifestations and required a lower dose of steroids.[313]

In the subsequent Phase III randomized controlled Belimumab International SLE Study-Subcutaneous (BLISS-SC) trial, 836 patients with active, autoantibody-positive SLE were randomized to receive weekly belimumab subcutaneously or placebo, in addition to standard SLE therapy.[314] This study showed that disease activity measured by SRI decreased in more patients treated with subcutaneous belimumab plus standard SLE care (60.8%) than in those receiving placebo plus standard SLE care (48.47%).

Other Available Targeted Therapies

A variety of biologics and targeted therapies are also used in SLE patients. These include tocilizumab, abatacept, tofacitinib, and anti-TNFs (for patients with co-existing RA).

Table 6 summarizes key information relating to the drugs used for the treatment of patients with SLE.

Table 6. Drugs used to treat SLE with recommended doses and contraindications

Drug	Dose	Contraindications	Potential Indications
Hydroxychloroquine	• ≤6.5 or ≤5 mg/kg/day, with a maximum dose of 400 mg/day • Renal insufficiency: 200 mg/day • Dialysis patients: 200 mg 3x/week following dialysis	• Hypersensitivity to HCQ, 4-aminoquinoline derivatives or any component of the drug • Development of HCQ retinopathy or any other HCQ side effect	• Cutaneous lupus • Lupus arthritis • Serositis • Renal lupus
Vitamin D	• Start at 50 000 IU/week Goal: 25(OH) vitamin D level of 40 ng/mL		• Global disease activity • Renal lupus • Promote bone health

DHEA-S	• 100-200 mg/day	• Hypersensitivity to DHEA or DHEAS or any of the drug components • Male gender or postmenopausal women • Children • Breast feeding women • Known or suspected pregnancy • Undiagnosed genital bleeding • History of breast cancer	• Constitutional symptoms • Cutaneous lupus • Lupus arthritis • Osteoporosis
Methotrexate	• 7.5-25 mg/week, orally or subcutaneously	• Hypersensitivity allergy to methotrexate • Pregnancy	• Lupus arthritis • Cutaneous lupus

Drug	Dose	Contraindications	Potential Indications
Leflunomide	• 10-20 mg/day orally • May be used if there is no risk of hepatotoxicity or bone marrow depression	• Hypersensitivity to leflunomide or any component of the drug • Pregnancy • Liver disease	• Lupus arthritis • Lupus nephritis
Azathioprine	• 1-2 mg/kg/day	• Hypersensitivity to azathioprine or any component of the drug	• Lupus arthritis • Lupus nephritis
Cyclophosphamide	• NIH .75–1.0 g/m^2 IV monthly for 6 months, then quarterly for up to 1 year after complete remission OR • Euro-Lupus 500 mg IV every 2 weeks for 6 doses	• Hypersensitivity to cyclophosphamide • Bone marrow depression • Pregnancy	• Lupus nephritis • CNS-SLE

Mycophenolate mofetil	• 2-3 g/day for 6 months with or without glucocorticoids, followed by maintenance with mycophenolate mofetil for 3 years	• Hypersensitivity to the drug or any of its components • Hypersensitivity to polysorbate 80 • Pregnancy • Women of child bearing age who are not using effective contraception • Breast feeding	• Lupus nephritis • Cutaneous lupus • Serositis • CNS-SLE
Tacrolimus	• .5 mg twice daily with gradual increments	• Known hypersensitivity to tacrolimus or any of the other drug components	• Lupus nephritis
Rituximab	• 1000 mg followed by repeat dose in 2 weeks	• Hypersensitivity to rituximab	• Lupus arthritis • Cutaneous lupus • Refractory lupus nephritis • CNS-SLE
Drug	**Dose**	**Contraindications**	**Potential Indications**
Belimumab	• 10 mg/kg IV on Days 0, 14, and 28; then every 28 days • Subcutaneously 200 mg/mL weekly	• Hypersensitivity to belimumab	• Cutaneous lupus • Lupus arthritis

CNS-SLE, neuropsychiatric lupus; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HCQ, hydroxychloroquine; IU, International Units; IV, intravenous; SSRIs, selective serotonin reuptake inhibitors

Monitoring

Frequency of Visits

Patients with SLE require lifelong monitoring to detect and treat flares as early as possible.[315] In general, the frequency of follow-up visits should be tailored to each patient depending on disease activity, severity of disease, type of treatment, response to treatment, and the need to monitor patients for possible medication toxicities. The 1999 ACR Guidelines[315] recommend that patients with stable, mild SLE may be followed up at 3 to 6 month intervals. According to the EULAR recommendation, patients with inactive disease without comorbidities or solid organ damage may be seen every 6 to 12 months.[65] More frequent visits are needed for patients with active disease, severe disease, or adverse reaction related to treatment; and for those with lupus nephritis or an increased risk of cardiovascular disease.

If immunosuppressive therapy is ongoing, patients should be seen more often.[315] All medications used for the management of SLE require monitoring for signs of toxicity. In addition to the monitoring tests

recommended for all patients with SLE and for those with renal involvement, the following list of medications and associated recommended laboratory testing[315] should be used as a guide:

- NSAIDs
  - CBC, at least annually ○ Creatinine, annually
- Glucocorticoids ○ Serum glucose or urine dipstick for glucose, every 3-6 months
  - Bone densitometry, every 1 to 2 years, based on the dose of steroids and other risk factors[316, 317]
  - Cholesterol, annually, with lipid panel, if abnormal
- Hydroxychloroquine ○ Retinal examination, baseline, 5 years, and then annually
- Azathioprine ○ CBC and platelet count, every 1-2 weeks when dose is increased, every 1 to 3 months thereafter
  - Aspartate aminotransferase, periodically ○ Papanicolaou (Pap) smear, every 1 to 3 years
- Cyclophosphamide ○ CBC and urinalysis, monthly ○ Urine cytology ○ Pap smear, annually
- Methotrexate ○ CBC and platelet count, every 4 to 12 weeks
  - LFTs, every 4 to 12 weeks ○ Serum creatinine every 12 weeks

A general follow-up evaluation for all patients may include but not be limited to the following:[65, 315]

- History and physical examination to evaluate features of SLE
- CBC including a platelet count and differential
- Creatinine and glomerular filtration rate (GFR) calculation
- Urinalysis and urine protein/creatinine ratio
- SLEDAI, Physician Global Assessment, and LLDAS (for treat-to-target)
- Anti-dsDNA
- C3 and C4 levels
- Antiphospholipid antibody tests can be repeated in certain situations, such as flare, after reduction in medications, or at time of thrombotic events

An observational cohort study followed 515 patients SLE for 2 years and demonstrated that those with mild or inactive disease should be followed with clinical and laboratory measures every 3 to 4 months.[318] The investigators noted that 25% of patients with asymptomatic SLE had variable silent laboratory abnormalities such as proteinuria, hematuria, pyuria, casts, low hemoglobin, leukopenia, thrombocytopenia, elevated serum creatinine, positive anti-DNA antibodies, and low complement.

Prior to pregnancy, SLE patients should have re-evaluation of anti-Ro, anti-La titers, and aPL antibodies in addition to the tests listed above.[65]

Patients treated with hydroxychloroquine are at risk of developing drug-induced retinopathy, which can lead to scotomata, and is the most serious side effect of this therapy.[319, 320] Early detection of this problem is important, particularly because it is asymptomatic early on and can be detected only through screening.[321] The risk of developing hydroxychloroquine retinopathy is increased with renal or hepatic dysfunction, obesity, age over 60 years old, preexisting retinal disease or maculopathy, a daily dose of hydroxychloroquine exceeding 400 mg or 6.5 mg/kg of ideal/lean body weight for short individuals, a cumulative dose exceeding 1000 g, or use of the drug for more than 5 years.[322]

Every patient to be started on hydroxychloroquine should undergo a baseline ophthalmologic examination consisting, at a minimum, of a visual field evaluation and a spectral-domain optical coherence tomography. Other helpful tests include an multifocal electroretinogram, microperimetry, and fundal autofluorescence.[124]

Renal Monitoring

All general monitoring recommendations for patients with SLE should be included in the follow up of patients who have renal involvement, especially of those with active nephritis. Patients with active nephritis may need to be seen monthly following diagnosis; and during induction therapy, relapse, and withdrawal of treatment. If there is no active nephritis, a visit every 3 months is needed for early identification of disease relapse.[67, 187, 323]

Regular monitoring of this subset of SLE patients should include at least the following:[67, 187]

- Body weight
- Blood pressure
- Serum creatinine and estimated GFR
- Serum albumin
- Proteinuria by urine protein/creatinine ratio
- Urinary sediment (microscopic evaluation)
- Serum C3/C4
- Serum anti-dsDNA antibody levels
- CBC and LFTs to monitor for toxicity
- Adherence checks such as therapeutic drug levels

Spot urinary protein/creatinine ratio is a valid measurement for assessing proteinuria.[324, 325] Timed (12- or 24-hour) urine collections may also be used at baseline and when major therapeutic changes are required.[187]

The reappearance of urine casts,[326] abnormal complement levels,[327, 328] anti dsDNA titers,[329-332] anti C1q,[333] and anti-nucleosome antibodies[334, 335] are important predictors of renal flare and can indicate the need for more monitoring.

Repeat renal biopsy is important in patients with relapse of nephritis after a complete renal response, or in those with refractory disease to guide the choice of therapy.[336-339]

Malignancy Screening

Recent advances in the management of SLE have led to improved survival and prolongation of life expectancy.[340] Consequently, chronic complications and organ damage such as cardiovascular disease and malignancy are encountered more frequently.[340, 341] The exact reason for an increased cancer risk in SLE is not completely understood. However, the link between SLE and cancer has been attributed to medication usage, viral infections (such as HPV), and inherent immune system abnormalities,[342] the overlap with clinical syndromes such as Sjögren's syndrome,[343] and the presence of traditional lifestyleassociated risk factors for cancer, especially smoking.[344]

Recent data from a multicenter international SLE cohort study with 16 409 patients showed that there was an increased risk of malignancy in patients with SLE when compared to the general population.[345] The investigators reported a significant risk of hematologic malignancies, particularly non-Hodgkin's lymphoma and leukemia. They also reported increased risks of cancer of the vulva, lung, thyroid, and hepatobiliary system. However, there was a decreased risk for breast, endometrial, and ovarian cancers.[345]

Hematologic Malignancies

A meta-analysis of five prospective cohort studies confirmed an increased risk of hematologic malignancy in patients with SLE. The most common malignancy observed was non-Hodgkin's lymphoma.[346] The most common type non-Hodgkin's lymphoma seen in SLE patients was diffuse B cell lymphoma.[345, 347]

Lung Malignancies

A meta-analysis of seven cohort studies confirmed an increased risk of lung cancer in patients with SLE.[348] In a multicenter cohort analysis, a history of smoking was found to be a strong predictor for lung cancer in patients with SLE.[349] Smoking has also been shown to be a predisposing factor for increased SLE disease activity,[348] and greater cumulative disease activity increases the risk of cancer.[350] According to the Swedish Hospital Discharge Registry, small cell lung cancer is the lung cancer most commonly found in patients with SLE.[351]

Cervical Cancer

The increased risk of cervical dysplasia and high-grade squamous intraepithelial lesions in SLE patients has been reported in a number of studies.[352, 353] In a meta-analysis of seven studies, a nine-fold increase in the risk of high-grade cervical squamous intraepithelial lesions in SLE was found.[352] However, in an international multicenter SLE cohort, which excluded cervical dysplasia and carcinoma *in situ*, whether an increased risk of invasive cervical cancer exists remained unclear.[345]

Patients with SLE have an increased risk for HPV, which increases the risk of developing cervical cancer.[353] In addition, immunosuppressive therapy, especially cyclophosphamide, may increase the risk of HPV infection and cervical dysplasia.[354-356] Consequently, EULAR recommends routine Pap smear screening for cervical dysplasia in female patients with SLE.[357]

Monitoring Risk Factors for Cardiovascular Disease

In the Hopkins Lupus Cohort, the risk of cardiovascular disease was found to be 2.66 times greater in patients with SLE than the general population.[111] Recent data from the SLICC inception cohort of 1848 patients found that, within 15 months of diagnosis, the prevalence of myocardial infarction was significantly higher in SLE patients than in healthy individuals. Cardiovascular disease may occur early or even before the diagnosis of SLE.[358] It may be appropriate to consider coronary computed tomography (or equivalent) 10 years after the diagnosis of SLE to identify atherosclerosis early.

Patients with SLE should be screened for both traditional modifiable and SLE-specific risk factors for cardiovascular disease. Traditional modifiable risk factors include:

- **Smoking**
  Smoking is a well-established risk factor for cardiovascular disease in the general population.[359] Patients with SLE who smoke were found to have a two- to three-fold greater risk of cardiovascular disease than non-smokers.[135, 360-363] Conversely, smoking is a risk factor for developing SLE.[364] In patients who already have SLE, smoking may lead to an increase in anti-dsDNA antibodies.[365] It may also interfere with the action of antimalarial drugs such as hydroxychloroquine.[366]

- **Hypertension**
  Hypertension is a major independent risk factor for coronary artery disease (CAD) in SLE.[360, 363, 367-373] It is also associated with arterial stiffness,[374, 375] progression of carotid plaques,[376-380] and poor renal outcome in patients with SLE.[381] Based on a 2016 report, the treatment target for hypertension is a blood pressure of 120/80.[382]

- **Hyperlipidemia**
  Hypercholesterolemia in SLE patients is a significant risk factor for CAD,[367, 369, 383-385] carotid plaque formation,[374, 377, 386] coronary artery calcification,[387] and myocardial perfusion defects.[373, 388]

  Elevated triglycerides[369, 389] and low HDL[372] are also independent predictors of cardiovascular disease in patients with SLE. In these patients, HDL may be proinflammatory and not protective as it is in healthy individuals.[379, 390]

- **Diabetes mellitus**
  Patients with diabetes and SLE have two to four times the risk for cardiovascular disease[111] and 60 times the risk for carotid artery plaque progression[390] when compared to SLE patients without diabetes.

- **Obesity**
  Obesity is a risk factor for hypertension, hyperlipidemia, Type 2 diabetes, cardiovascular disease, and obstructive sleep apnea.[391] Obese SLE patients have a higher risk of cardiovascular disease, coronary artery calcification,[392, 393] and carotid plaque formation.[394, 395]

Patients with SLE should also be screened for the following SLE-specific risk factors:

- **Auto-antibodies**

  In patients with SLE, increased rates of cardiovascular disease have been related to past levels of disease activity, recent elevated levels of circulating anti-dsDNA, the presence of antiphospholipid antibodies, elevated levels of CRP, and current use of at least 10 mg/day of corticosteroids.[111] In addition, patients with SLE and anti-cardiolipin antibodies have increased rates of noncalcified coronary artery plaque.[135, 396] This type of plaque can rupture and result in acute coronary artery obstruction and potentially in myocardial infarction.

- **Renal disease**

  Impaired renal function is a well-defined atherosclerosis risk factor in the general population.[397]

- **Medications** ○ *Corticosteroids*

  The use of corticosteroids at doses ≥10 mg/day increases the risk of cardiovascular disease in patients with SLE.[111]

  - *Immunosuppressive drugs*

    The use of azathioprine may increase the risk of cardiovascular disease in SLE patients.[111] One paper reported that azathioprine increased the risk of developing increased carotid intimal-medial thickness.[394]

  - *NSAIDs*

    The use of indomethacin at doses of at least 150 mg/day has been shown to decrease GFR by approximately 16% in patients with SLE and initially normal or slightly impaired GFR.[398] Indomethacin should be avoided in patients SLE, because it may put them at risk of developing renal insufficiency. In addition, the use of NSAIDs is associated with an increased risk of cardiovascular disease in the general population.

  - *Hydroxychloroquine*

    In contrast to all other medications, hydroxychloroquine has shown a protective effect against cardiovascular disease in patients with SLE.[384, 399]

Reproductive/Hormonal Issues

Contraception

As pregnancy confers a significantly increased risk of lupus nephritis, pre-eclampsia, preterm birth and even mortality,[400] family planning is an essential part of the management of pre-menopausal women with SLE. While treated with medications that are teratogenic, completely effective contraception is required. These medications include angiotensin-converting-enzyme (ACE) inhibitors, statins, mycophenolate mofetil, methotrexate, possibly leflunomide, and cyclophosphamide. For mycophenolate mofetil, having the patient read and sign the FDA Risk Evaluation Management Strategy (REMS) form is recommended.[401] Preferred methods of contraception with less than a 1% failure rate include the intrauterine contraceptive device (IUD) ParaGard® (with 12-year efficacy). Hormonal IUDs include Skyla® and Mirena® (levonorgestrel). The hormonal implant is Nexplanon® (etonogestrel).

The second tier includes oral contraceptives, the patch, the ring, and Depo-Provera®. The SELENA study showed that oral contraceptives did not increase lupus flares; however, oral contraceptives should not be used in women with very active lupus, hypercoagulability, elevated liver function tests, and migraines.[402] In addition, mycophenolate mofetil interferes with the efficacy of oral contraceptives.

Rheumatologists should be able to give general advice about emergency contraception and , in particular, insist that patients have an emergency gynecologic appointment. The ParaGard IUD is 100% effective within 5 days. Ella® (ulipristal acetate) works up to 5 days but is less effective in women with body weights over 195 lbs. Plan B One-Step® is effective up to 3 days, but less effective in women with weighing over 165 lbs.

Preparing for Pregnancy

Unfortunately, 50% of pregnancies are unplanned. The goal in SLE is for pregnancy to occur only when the SLE is well controlled on allowable medications. It is particularly important to plan ahead when a woman has lupus nephritis. It is likely that she will be on mycophenolate mofetil, which must be stopped 3 months prior to pregnancy with a switch to azathioprine and/or tacrolimus. The 3-month timespan will allow assessment if the new regimen is controlling the lupus nephritis before conception. Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and statins must be stopped BEFORE conception. Methotrexate, likely leflunomide, cyclophosphamide, and belimumab should be stopped before conception. Hydroxychloroquine should be continued to control lupus, and because it reduces pregnancy complications.[147]

Lupus nephritis is more likely to flare in pregnancy. Women should be seen every 6 weeks. Patients with anti-Ro and/or La will need fetal cardiac ultrasounds from the 16th week of gestation. Hydroxychloroquine may reduce the risk of congenital heart block.[150] Women with aPL antibodies (the lupus anticoagulant being the most important) and no previous pregnancy or past successful pregnancies should be on aspirin and hydroxychloroquine. If more than one or two first trimester losses or even one late loss, prophylactic low molecular weight (LMW) heparin twice daily and low-dose aspirin is recommended. In women with a past history of thrombosis, therapeutic LMW heparin is given. Low molecular weight heparin must be transitioned to unfractionated heparin prior to delivery.

Lupus Manifestations in Specific Organ Systems

Lupus Nephritis

Note: The pharmacologic management of lupus nephritis is complex. Treatment is composed of an induction phase and a maintenance phase. In addition to the United Rheumatology Guidelines, providers should carefully review the ACR *and/or* Joint EULAR/ERA-EDTA Recommendations for the Management of Adult and Pediatric Lupus Nephritis *guidelines cited in the narrative below for a more detailed description of medications, routes of administration, dosing, and duration of treatment.*

Lupus nephritis, is defined as proteinuria of >.5 gm/day or >3+ by dipstick and/or cellular casts including red blood cells (RBCs), hemoglobin, granular, tubular or mixed. Fifty percent to 60% of SLE patients will develop lupus nephritis within 10 years of diagnosis.[67, 403, 404]

In 2012, three guidelines for the treatment of lupus nephritis were published:

- Joint EULAR/ERA-EDTA Recommendations for the Management of Adult and Pediatric Lupus

Nephritis[187]

- ACR Guidelines for Screening, Treatment, and Management of Lupus Nephritis[67]
- Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis[323]

Treatment of lupus nephritis is based on the classification of the disease using the International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis Criteria.[405]

Treatment of Class I Lupus Nephritis

No treatment is required for this group of SLE patients, who have minimal disease.

Treatment of Class II Lupus Nephritis

The ACR guideline recommends that Class II lupus nephritis generally does not require immunosuppressive treatment. All lupus nephritis patients with proteinuria ≥.5 g/24 hours should be treated with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), both of which reduce proteinuria by approximately 30%, and significantly delay doubling of serum creatinine and progression to end-stage renal disease.[67]

On the other hand, EULAR/ERA-EDTA[187] recommended low to moderate doses of oral steroids (.25-.5 mg/kg/day) alone or in combination with azathioprine (1–2 mg/kg/day). Azathioprine could be used in cases of proteinuria over 1 g/24 hours, especially in the presence of glomerular hematuria or as a steroid-sparing agent. Practically, however, mycophenolate mofetil is used.

Treatment of Class III and IV Lupus Nephritis

Proliferative lupus nephritis (Class III – focal proliferative – and Class IV – diffuse proliferative) is an important cause of end stage renal disease in SLE patients.[191] Treatment of proliferative lupus nephritis is divided into an induction phase, followed by maintenance phase. It is recommended that at least 3 years of immunosuppressive maintenance treatment be used to achieve remission and better long-term outcomes.[191, 406]

Guidelines recommend either cyclophosphamide or mycophenolate mofetil induction regimens, but differ in the amount of IV corticosteroid given at the initiation of therapy, the use of oral prednisone for maintenance, and the aggressiveness of tapering the drugs.[67, 187, 323] Physicians should consult either the ACR or EULAR/ERA-EDTA guidelines for details about the use of steroid doses. However, newer regimens such as *Rituxilup*[407] (rituximab followed by mycophenolate with no oral steroid) include no oral prednisone. In the recent Phase 2 lupus nephritis randomized clinical trial of voclosporin, a new calcineurin inhibitor, only 25 mg of prednisone was used.[408, 409]

Mycophenolate mofetil is preferred over cyclophosphamide in African and Hispanic patients, based on a *post hoc* subgroup analysis of the ALMS trial.[410]

Mycophenolate mofetil is also preferred for young lupus nephritis patients who have a major concern with fertility preservation, because high-dose cyclophosphamide may cause infertility.[230, 411]

Patients who fail to respond to a 6-month trial of treatment with glucocorticoids plus either mycophenolate mofetil or cyclophosphamide could be switched to either cyclophosphamide or

mycophenolate mofetil, which ever drug has not been used. When starting with the new drug choice, IV steroids for 3 days are recommended.[67, 187] Providers should consult either the ACR or EULAR/ERA-EDTA guidelines for more details. However, many counsel adding tacrolimus or rituximab in mycophenolate partial or non-responders.

Both guidelines[67, 187] recommend mycophenolate mofetil (1–2 g/day) or azathioprine (1.5-2.5 mg/kg/day) for the maintenance phase of treatment. The EULAR/ERA-EDTA guideline[187] recommends mycophenolate mofetil in patients who responded to it as part of the induction phase, based on results of the ALMS[191] and MAINTAIN Nephritis[193] trials. For those having difficulty tolerating mycophenolate from a GI standpoint, an enteric coated agent (Myfortic®) can be used (usual dose is 720 mg twice a day).

A recent systematic review and meta-analysis included six randomized controlled trials to determine the most effective immunosuppressive therapy for the long-term maintenance phase of proliferative lupus nephritis. The authors focused on the comparative effectiveness of cyclophosphamide versus azathioprine versus mycophenolate mofetil, based on the incidence of renal failure with these regimens; they found no conclusive evidence of the superiority of one drug over the others.[229]

A subsequent systematic review and meta-analysis of randomized controlled trials of different treatments of lupus nephritis was published in 2016.[202] The goal of this review was to compare the efficacy and harms of different lupus nephritis induction and maintenance regimens. This review reported that the incidence of end stage renal disease was lower in patients treated with

- Either cyclophosphamide or cyclophosphamide and azathioprine when compared to standard-dose corticosteroids
- High-dose cyclophosphamide when compared to high-dose corticosteroids

There was no difference in the outcomes of patients treated with any of the immunosuppressive drugs to treat lupus nephritis (cyclophosphamide, azathioprine, mycophenolate mofetil, and tacrolimus), except for a decrease in the occurrence of relapse with mycophenolate mofetil when compared to azathioprine. The authors also found no difference among these drugs with respect to the risk of malignancy, diabetes, aseptic necrosis, nausea, or death. There was a difference in the occurrence of other side effects or adverse events among the immunosuppressive drugs:[202]

- Cyclophosphamide was associated with a 4.5 times increase in alopecia when compared to mycophenolate mofetil (may be relative when treating younger patients).
- High-dose cyclophosphamide was associated with a 3.3-times increase in the odds of developing GI complaints when compared to mycophenolate mofetil and an 8.2-times increase in the odds of developing it when compared to tacrolimus.
- Cyclophosphamide was associated with a 9.7 times higher odds of developing urinary bladder toxicity when compared to corticosteroids.

Treatment of Class V Lupus Nephritis (Diffuse Membranous Nephritis)

Immunosuppressive therapy is recommended for Class V lupus nephritis with proteinuria (>3 g/24 hours).[187, 412] However, earlier treatment leads to better response.[146]

Both the EULAR/ERA-EDTA[187] and ACR[67] guidelines prefer mycophenolate mofetil over the other immunosuppressive agents (IV cyclophosphamide, CNIs, azathioprine, or rituximab) for induction and

maintenance therapy at appropriate doses. The preference for mycophenolate mofetil is mainly based on a combined retrospective analysis of two randomized controlled trials, showing that mycophenolate mofetil taken at a total daily dose of 2 to 3 g plus daily prednisone for 6 months and IV cyclophosphamide (.5-1.0 mg/kg monthly) plus prednisone for 6 months resulted in similar improvement.[413]

In addition, a retrospective cohort study evaluated the efficacy of mycophenolate mofetil therapy in membranous lupus nephritis patients with and without a concurrent proliferative lesion.[414] This study reported that, at 12 months, mycophenolate mofetil induced and maintained complete remission in a significant proportion of patients with membranous lupus nephritis without coexistent proliferative lesions, particularly in those with mild proteinuria.[414]

The efficacy of tacrolimus, cyclosporine, and rituximab in idiopathic membranous nephropathy supports a therapeutic role for these agents in some patients with membranous lupus nephritis.[415-417] If patients fail to respond to cyclophosphamide or mycophenolate mofetil then, according to the EULAR/ERA-EDTA guidelines,[187] they may be switched to the drug which has not been used, or rituximab may be tried.

Rituximab without Oral Corticosteroids

Eliminating or decreasing the long-term use of oral glucocorticoids in the lupus nephritis population was the target of a study reported in the *Annals of Rheumatic Diseases* in 2013.[299] Condon and colleagues at Hammersmith Hospital in the United Kingdom reported on the results of an observational study of 50 patients with Class III, IV, or V lupus nephritis using the medication protocol *Rituxilup* (rituximab and mycophenolate mofetil without oral steroids). During the induction phase, patients were treated with 1 g of rituximab plus 500 mg of IV methyl prednisolone on Days 1 and 15. Mycophenolate mofetil without oral steroids was used for the maintenance phase. In addition, ARBs and ACE inhibitors were used at the highest tolerable dose. Complete or partial remission was achieved by 62% of the patients by 26 weeks. This development should be monitored carefully, due to its potential of achieving equal or better results than the current drug combinations and to decrease or eliminate the negative effects of long-term steroid use. Reports on larger groups of patients from different centers followed for longer intervals are required.

Other Manifestations

Treatment recommendations for patients with SLE manifestations in additional organ systems are summarized in Table 7.

Table 7. Treatment of other potential manifestations of SLE

Type of Manifestation	Treatment
Hematologic Manifestations	

Autoimmune hemolytic anemia[418-425] (Elevated reticulocyte count, low haptoglobin, increased indirect bilirubin, high LDH, and a positive direct Coombs test)	**Mild** • Mild increase in prednisone • Assessment 1 week later **Moderate and severe** • IV methylprednisolone 1000 mg daily for 3 days followed by oral prednisone • IVIG • Azathioprine or mycophenolate mofetil as maintenance therapy • Rituximab for refractory cases • Splenectomy for refractory cases

Type of Manifestation	Treatment

Thrombocytopenia[291, 426-450]	**1st line** • Treatment is not needed if platelet count is >30,000 • IV or oral corticosteroids • Platelet transfusions should be considered only when the platelet count is less than $10 \times 10^9/mm^3$ or invasive procedures are needed. **2nd line** In refractory cases and as steroid sparing agents: • Azathioprine • Mycophenolate mofetil **3rd line** • Rituximab • Splenectomy showed good short-term response in SLE patients. However, many patients relapsed. **In emergency situations (**e.g., emergency therapy or active bleeding) • IVIG • Eltrombopag or romiplostim • Thrombopoeitin receptor agonists, which increase platelet production. They increase the risk of thrombosis.
Leucopenia[451, 452]	Rarely requires therapy • Glucocorticoids are the main treatment for leukopenia in SLE patients. • Cyclosporine or tacrolimus can be used as a steroid sparing agent. • G-CSF should be avoided in SLE patients as it can precipitate severe flares.[452]

Type of Manifestation	Treatment
Nervous System Manifestations	

Neuropsychiatric Lupus[66, 192, 207, 208, 210-213, 277, 296, 297, 453-461]	**1st line** • Glucocorticoids Pulse methylprednisolone 1,000 mg intravenously for 3 consecutive days followed by oral prednisone. If psychosis present, corticosteroids need to be limited. • IV cyclophosphamide • Azathioprine or mycophenolate mofetil used as maintenance therapy following cyclophosphamide. **2nd line** • Rituximab in severe refractory cases • IVIG used in severe refractory cases and considered as a first line in the presence of concomitant infection and in pregnant females. **3rd line** • Plasma exchange in combination with immunosuppressive therapy
Immune System Manifestations	
Antiphospholipid Syndrome	• Heparin followed by warfarin (DOACs not recommended [462-465]) **Catastrophic APS** • IV methylprednisolone, heparin, plasmapheresis (or IVIG) • Rituximab or eculizumab
Antiphospholipid Antibody **Prophylactic Treatment**	• Antiplatelet: acetylsalicylic acid (aspirin) 81 mg/day • Hydroxychloroquine • Vitamin D • Statin

Type of Manifestation	Treatment

Cutaneous Manifestations	

Cutaneous lupus erythematosus[131, 466-478]	**1st line**
	• Sun block (must block both UV-A and UV-B) and sun avoidance
	• Topical corticosteroid should be used at the lowest potency and for the shortest duration. It is preferable to use:
	  ○ Low-mid-potency corticosteroid on the face
	  ○ Mid-potency corticosteroid (e.g., triamcinolone acetonide, betamethasone valerate) on the trunk and extremities
	  ○ High-potency corticosteroid (e.g., Clobetasol) on the palms and soles
	• Topical CNIs
	• Hydroxychloroquine or chloroquine Hydroxychloroquine and quinacrine may be given concurrently.
	• Systemic corticosteroids as bridging therapy.
	Short courses or low doses of oral steroids can be given in acute cases and as a bridge until the benefit of antimalarial drugs kicks in.
	2nd line
	• Methotrexate
	• Mycophenolate mofetil
	• Azathioprine
	3rd line
	• Dapsone
	• Rituximab

Type of Manifestation	Treatment
Pulmonary Manifestations	

Diffuse alveolar hemorrhage[479, 480]	**1st line** • Pulse methylprednisolone 1,000 mg daily for 3 days followed by 1 mg/kg oral **2nd line** • Cyclophosphamide • Plasmapheresis • Rituximab
Lupus pulmonary arterial hypertension[481-485]	**1st line** • General treatment of primary pulmonary hypertension to include sildenafil, endothelin receptor antagonists, and prostacyclin as appropriate. • IV and/or oral glucocorticoids and IV cyclophosphamide if due to active lupus • Azathioprine or mycophenolate mofetil used as a maintenance therapy following cyclophosphamide. • Anticoagulation if antiphospholipid antibodies are present **2nd line** • Rituximab

Type of Manifestation	Treatment
Joint Manifestations	

Lupus arthritis[132, 177, 192, 232, 238, 308, 486-490]	**1st line** • Hydroxychloroquine • Short-term, low-dose prednisone <6 mg daily • NSAID • Medrol dose pack or IM triamcinolone 100 mg for flare **2nd line** • Methotrexate • Leflunomide • Azathioprine **3rd line** • Rituximab • Belimumab, particularly if low complement or high anti-DNA • Anti-TNF, if true co-existing RA
Cardiac Manifestations	
Lupus pericarditis[491-493]	**Mild and moderate pericarditis** • NSAID • Corticosteroids, IV or oral • Hydroxychloroquine • Mycophenolate mofetil **Cardiac tamponade** • Pulse methylprednisolone, usually followed by mycophenolate mofetil • Pericardial window **Recurrent pericarditis** • Colchicine • Methotrexate • Azathioprine • Mycophenolate mofetil
Type of Manifestation	**Treatment**

Lupus myocarditis[494-499]	**1st line** • Pulse methylprednisolone followed by oral prednisone 1 mg/kg **2nd line** • IV cyclophosphamide • Azathioprine or mycophenolate mofetil as maintenance therapy **3rd line** • IVIG • Plasmapheresis • Rituximab

APS, antiphospholipid syndrome; DNA, deoxyribonucleic acid; DOAC, direct oral anticoagulant G-CSF, granulocyte-colony stimulating factor; INR, international normalized ratio; IV, intravenous; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor

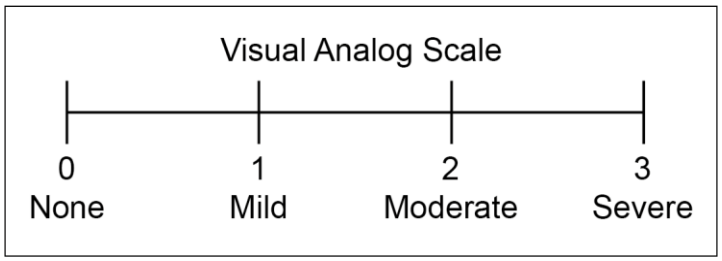
Lupus During Pregnancy

The first-line treatment for pregnant patients is hydroxychloroquine,[147] as it is both safe and desirable (it reduces pre-eclampsia and disease activity) in pregnancy. When renal manifestations are present, azathioprine or tacrolimus[263] are appropriate choices. Flares during pregnancy can be effectively managed with IV methylprednisolone pulses. When immunosuppressives are needed cyclosporine, tacrolimus and azathioprine can be used.

Appendix

Systemic Lupus Erythematosus Disease Activity Index Selena Modification

Physicians Global Assessment (PGA)[402]


Visual Analog Scale
0
None
1
Mild
2
Moderate
3
Severe

SLE Disease Activity Index (SLEDAI)[402]

Check box: If descriptor is present at the time of visit or in the proceeding 10 days

Wt or Score	Present	Descriptor	Definition
8	☐	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	☐	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
8	☐	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
8	☐	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐	Lupus Headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion)
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary Casts	Heme-granular or red blood cell casts

4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	New onset or recent increase of more than .5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
Wt or Score	**Present**	**Descriptor**	**Definition**
2	☐	Rash	Ongoing inflammatory lupus rash.
2	☐	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	☐	Mucosal Ulcers	Ongoing oral or nasal ulcerations due to active lupus.
2	☐	Pleurisy	Classic and severe pleuritic chest pain with pleural rub or effusion or pleural thickening due to lupus.
2	☐	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	☐	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	☐	Fever	>38˚C. Exclude infectious cause
1	☐	Thrombocytopenia	<100 000 platelets/mm^3
1	☐	Leukopenia	<3000 WBC/mm^3. Exclude drug causes

_____ TOTAL SCORE (Sum of weights next to descriptors marked present)

SELENA Flare Index

Mild or Moderate Flare	Severe Flare
Change in SLEDAI >3 points	Change in SLEDAI >12 points
New/worse: _Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus _Nasopharyngeal ulcers _Pleuritis _Pericarditis _Arthritis _Fever (SLE)	New/worse: _CNS-SLE _Vasculitis _Nephritis _Myositis _Platelets <60,000 _Hemolytic anemia: Hb <7% or decrease in Hb >3% **_Requiring**: double prednisone or prednisone >.5 mg/kg/day
Increase in Prednisone, but not to >.5 mg/kg/day	Prednisone >.5 mg/kg/day
Added Plaquenil	New Cytoxan, Azathioprine, Methotrexate, Cellcept, Hospitalization (SLE)
≥I increase in PGA, but not to more than 2.5	Increase in PGA to >2.5

CNS-SLE, neuropsychiatric lupus; Hb, hemoglobin; PGA, Physician Global Assessment; Pk, platelets; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index

Lupus Low Disease Activity State (LLDAS)[500]

- SLEDAI 4, PGA 1
- Prednisone <=7.5 mg/day
- No major organ involvement (renal, CNS, serositis, vascular, or constitutional) • No recent increase in disease activity

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Document Updates

Document Version	Description of Changes	Approval Date
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