BMJ Best Practice

Systemic lupus erythematosus

Straight to the point of care

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Summary

Systemic lupus erythematosus (SLE) is a generalized disorder that can affect any system.

Symptoms and signs may accumulate over time.

The diagnosis is made using 2019 criteria recommended by the American College of Rheumatology and the European League Against Rheumatology.

Treatments for mild to moderate serositis or arthritis include hydroxychloroquine, nonsteroidal anti-inflammatory drugs, or corticosteroids.

Treatments for more severe disease may include azathioprine, belimumab, cyclophosphamide, methotrexate, mycophenolate, rituximab, or tacrolimus.

Definition

SLE is a chronic multisystem disorder that most commonly affects women during their reproductive years. It is characterized by the presence of antinuclear antibodies. In addition to constitutional symptoms, it most frequently involves the skin and joints, although serositis, nephritis, hematologic cytopenias, and neurologic manifestations may occur during the course of the disease.

Earlier diagnosis and better management have resulted in a lower prevalence of life-threatening disease.

Epidemiology

SLE presents a significant disease burden worldwide. The incidence and prevalence of SLE are affected by gender, race, and ethnicity.[6] [7] Methods applied to study the epidemiology of SLE have limitations. Studies have primarily focused on white populations and most have been conducted in small, well-defined geographic areas.

The highest reported incidence of SLE is in North America (23.2 per 100,000 person-years), and the lowest reported incidences are in Africa and the Ukraine (0.3 per 100,000 person-years).[6] In the UK, the incidence of SLE has been estimated to be 4.91 per 100,000 person-years.[8]

Incidence is higher in women than in men; reported sex ratios range from 2:1 to 15:1.[8] [9] [10] Peak age of onset ranges from 30 to 70 years in women and between 50 and 70 years in men.[6] [8]

The Centres for Disease Control and Prevention National Lupus Registries estimated the prevalence of SLE in the US at 72.8 per 100,000 person-years.[11] The prevalence estimate was nine times higher among women than among men (128.7 per 100,000 versus 14.6 per 100,000, respectively). Prevalence was highest among African Americans (230.9 per 100,000 and 26.7 per 100,000 for women and for men, respectively), followed by Hispanics (120.7 per 100,000 and 18.0 per 100,000, respectively), and lowest in white populations (84.7 per 100,000 and 8.9 per 100,000, respectively).[11] Global epidemiologic data appear to confirm differences reported between ethnic groups in the US.[6]

Evidence suggests that prevalence of SLE in the UK is increasing.[6] [8]

Etiology

The etiology of SLE is not known but the interaction of an environmental agent in a genetically susceptible host is thought to be fundamental. The strong female preponderance also suggests a role for hormonal factors.[12] [13]

Genetic factors

Familial aggregation and higher-than-expected rates of concordance in twin studies suggest that genetic factors are important.[14] [15] The heritability of SLE has been estimated to be 43.9%.[16]

Genome-wide association studies have identified more than 60 genetic risk loci.[17] Predisposing genes may activate the innate or adaptive immune response, or have a potential role as self-antigen for autoreactive B cells.[18] Consistently reported SLE-associated loci include:[19] [20] [21] [22] [23] [24]

- IRF5 (interferon regulatory factor 5), which codes a transcription factor involved in the regulation of the expression of pro-inflammatory cytokines by several cell types
- STAT4 (signal transducer and activator of transcription 4), which acts as a transcription activator; essential for mediating responses to interleukin-12 in lymphocytes, and regulating the differentiation of T helper cells
- BANK1 (B-cell scaffold protein with ankyrin repeats 1), which encodes a B-cell-specific scaffold protein; may contribute to lupus by altering B-cell signaling
- ITGAM (integrin alpha M); significant association between ITGAM gene polymorphism and SLE in multiple ethnic populations
- PTPN22 (protein tyrosine phosphatase, nonreceptor type 22), a regulator of immune homeostasis through inhibition of T-cell receptor signaling and by selectively promoting type I interferon responses;

associated with autoimmune disease; a missense single-nucleotide polymorphism is associated with increased risk for SLE.

Environmental factors

The association may be noninfectious or infectious.

The most important noninfectious causative agents are drugs.[25] The first reported association was with procainamide, but other commonly implicated drugs include minocycline, terbinafine, sulfasalazine, isoniazid, phenytoin, and carbamazepine.[26] [27] [28] [29] [30] [31] [32] [33]

Pathogens most frequently associated with SLE include Epstein-Barr virus, parvovirus B19, cytomegalovirus, and human immunodeficiency virus type 1.[34] [35] [36] Potential mechanisms facilitating autoreactivity remain unclear; immunologic changes subsequent to infection and molecular mimicry have been proposed.[34] Further studies are required to determine whether infectious agents are causative agents.

Pathophysiology

SLE is primarily an antigen-driven immune-mediated disease characterized by high-affinity immunoglobulin G antibodies to double-stranded DNA, as well as nuclear proteins. Genes implicated in SLE may contribute to pathology by breaching immune tolerance and promoting autoantibody production.[37]

Rapid clearance of cells through apoptosis typically prevents exposure of nuclear antigens to the immune system. However, failure of this process, and that of other mechanisms that confer immune tolerance to nuclear antigens, may provoke an immune response.[37] [38] Loss of immune tolerance in this manner is evidenced by the presence of antinuclear antibodies.

NETosis, cell death in which neutrophil extracellular traps are released, is increasingly recognized as a source of nuclear antigens and bioactive molecules that may facilitate autoimmunity in SLE.[39]

While animal models have been used to illustrate how genes that affect autoantigen clearance can promote the production of antinuclear autoantibodies, evidence in humans remains limited.

Several mechanisms have been proposed, by which T-cell dysregulation of B cells may arise, resulting in autoimmunity.

Classification

2019 European League Against Rheumatism/American College of Rheumatology classification system[1]

Entry criterion

- Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)
- If absent, do not classify as SLE; if present, apply additive criteria

Additive criteria

- Additive criterion should not be counted if there is a more likely explanation than SLE
- Occurrence of a criterion on at least one occasion is sufficient
- SLE classification requires at least one clinical criterion and ≥10 points

- Criteria need not occur simultaneously
- Within each domain, only the highest criterion is counted toward the score*

Clinical domains and criteria

Constitutional

- Fever, 2 points

Hematologic

- Leukopenia, 3 points
- Thrombocytopenia, 4 points
- Autoimmune hemolysis, 4 points

Neuropsychiatric

- Delirium, 2 points
- Psychosis, 3 points
- Seizure, 5 points

Mucocutaneous

- Nonscarring alopecia, 2 points
- Oral ulcers, 2 points
- Subacute cutaneous OR discoid lupus, 4 points
- Acute cutaneous lupus, 6 points

Serosal

- Pleural or pericardial effusion, 5 points
- Acute pericarditis, 6 points

Musculoskeletal

- Joint involvement, 6 points

Renal

- Proteinuria >0.5 g/24 hours, 4 points
- Renal biopsy class II or V lupus nephritis, 8 points
- Renal biopsy class III or IV lupus nephritis, 10 points

Immunology domains and criteria

Antiphospholipid antibodies

- Anticardiolipin antibodies OR anti-beta2-glycoprotein 1 antibodies OR lupus anticoagulant, 2 points

Complement proteins

- Low C3 OR low C4, 3 points
- Low C3 AND low C4, 4 points

SLE-specific antibodies

- Anti-double-stranded (ds)DNA antibody** OR anti-Smith antibody, 6 points

Total score

Scores of 10 or more are classified as systemic lupus erythematosus if the entry criterion has been fulfilled.

* Additional criteria items within the same domain will not be counted.

** In an assay with ≥90% specificity against relevant disease controls.

1997 update of the 1982 American College of Rheumatology revised criteria for the classification of SLE[2] [3]

These criteria were initially developed to identify patients for clinical studies and were based on a white population. Any ≥4 of the 11 criteria are required to classify a patient as having SLE. These criteria can be present serially or simultaneously during any interval of observation.

1. Malar rash
    - Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. Discoid rash
    - Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3. Photosensitivity
    - Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers
    - Oral or nasopharyngeal ulceration, usually painless, observed by physician.
5. Arthritis
    - Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion.
6. Serositis (one of the following):
    - Pleuritis: convincing history of pleuritic pain, pleural rubs on auscultation, or evidence of pleural effusion
    - Pericarditis: documented by ECG, pericardial rub, or evidence of pericardial effusion.
7. Renal disorder (one of the following):
    - Persistent proteinuria >0.5 g/day or >3+ if quantification not performed
    - Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed.
8. Neurologic disorder (one of the following):
    - Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
    - Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance).
9. Hematologic disorder (one of the following):
    - Hemolytic anemia: with reticulocytes
    - Leukopenia: <4000/mm^3 on ≥2 occasions
    - Lymphopenia: <1500/mm^3 on ≥2 occasions
    - Thrombocytopenia: <100,000/mm^3 in the absence of offending drugs.
10. Immunologic disorder (one of the following):
    - Anti-DNA: presence of antibody to native DNA in abnormal titer
    - Anti-Smith: presence of antibody to Smith nuclear antigen

- Positive findings of antiphospholipid antibodies based on:
    - An abnormal serum level of IgG or IgM anticardiolipin antibodies
    - Positive test result for lupus anticoagulant using a standard method
    - A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.

11. Antinuclear antibody (ANA)
    - An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome.

2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus[4]

The SLICC criteria for SLE classification requires:

1. Fulfillment of at least 4 criteria, with at least one clinical criterion AND one immunologic criterion

   OR
2. Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Clinical criteria:

- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers: palate
- Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
- Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and 30 minutes or more of morning stiffness
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leukopenia (<4000/mm^3 at least once)
- Thrombocytopenia (<100,000/mm^3) at least once.

Immunologic criteria:

- ANA above laboratory reference range
- Anti-dsDNA above laboratory reference range, except enzyme-linked immunosorbent assay: twice above laboratory reference range
- Anti-Smith
- Antiphospholipid antibody: any of the following
- Low complement
- Direct Coombs test in the absence of hemolytic anemia.

Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of

definitions, and modified National Institutes of Health activity and chronicity indices[5]

- Class I: minimal mesangial lupus nephritis
- Class II: mesangial proliferative lupus nephritis
- Class III: focal lupus nephritis
- Class III (A): active lesions - focal proliferative lupus nephritis
- Class III (A/C):
    - Active and chronic lesions: focal proliferative and sclerosing lupus nephritis class III (C)
    - Chronic inactive lesions: focal sclerosing lupus nephritis
- Class IV: diffuse lupus nephritis
- Class V: membranous lupus nephritis
- Class VI: advanced sclerosis lupus nephritis.

Case history

Case history #1

A 16-year-old black female presents to her primary care physician with symptoms of fatigue, musculoskeletal pain, and a facial rash. On examination she is noted to be thin with malar skin changes. No other abnormality is found.

Case history #2

A 38-year-old white woman presents to the emergency department with 24 hours of dyspnea and pleuritic chest pain. On further questioning, she reports a 3-year history of Raynaud disease, polyarthralgia, and intermittent migraine. Physical examination reveals hypoxia, tachycardia, and normal blood pressure. Ventilation perfusion scanning confirms a pulmonary thromboembolism.

Other presentations

Most patients present with symptoms of fatigue, typical rash and/or musculoskeletal symptoms. Other symptoms and signs at presentation may include headaches or lymphadenopathy (cervical or axillary). Patients may present with pleuritis or pericardial effusions. Uncommon presentations include severe serositis or organ manifestations such as nephritis, possibly following triggers such as sun exposure or infection.

Approach

There are no internationally validated diagnostic criteria for SLE.

In a validation cohort, the 2019 European League Against Rheumatism/American College of Rheumatology (ACR) classification criteria had a sensitivity of 96.1% and specificity of 93.4%.[1] Comparable figures for the ACR 1997 criteria were 82.8% sensitivity and 93.4% specificity, and for the Systemic Lupus International Collaborating Clinics 2012 criteria were 96.7% sensitivity and 83.7% specificity.[1]

Constitutional symptoms and signs

Fatigue, fever, and weight loss are common symptoms that occur at some time during the course of the disease.

Fatigue is common, occurring in 80% to 100% of patients, but it does not correlate with disease activity.[48] [49] Fatigue from other causes, such as anemia, hypothyroidism, medications (e.g., beta-blockers), depression, fibromyalgia, and social stresses, should be considered.

Unexplained fever is common and characteristic for SLE.[1] It is thought to represent active disease. Exclusion of infection is important before initiating immunosuppressive therapy in a patient with SLE to prevent reactivation or exacerbation of chronic infection.[50] Fever persisting despite treatment with a nonsteroidal anti-inflammatory drug or acetaminophen should raise suspicion for an infectious or drug-related etiology. All patients presenting with persistent fever should have an appropriate symptom-targeted infection screen.

Weight loss in SLE may be related to disease activity or its treatment. Patients with SLE may have esophageal hypomotility leading to dysphagia. Vomiting and diarrhea may contribute to weight loss. SLE is associated with an increased risk for cancer, and this should be considered as a potential cause of weight loss.

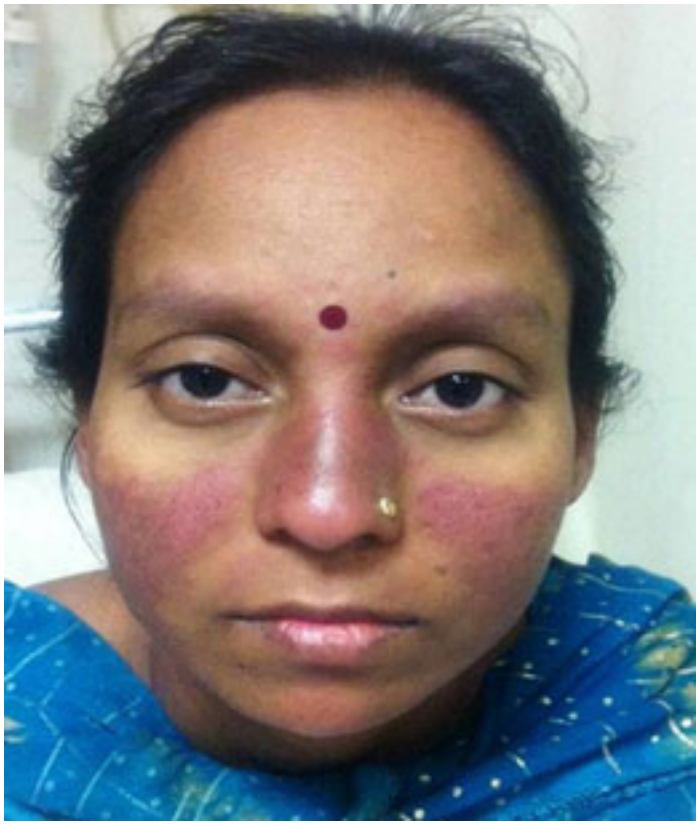
Lymphadenopathy

Peripheral lymphadenopathy is more often regional than generalized. The nodes are usually nontender, vary in size from shotty (clusters of small lymph nodes, each a few mm) to 3 to 4 cm, and are often in the cervical and axillary regions. Hilar lymphadenopathy is uncommon. Patients with lymphadenopathy are more likely to have constitutional manifestations. Lymphoma and infectious mononucleosis should be excluded. Histology of lymph node biopsies in SLE frequently shows reactive hyperplasia.

Mucocutaneous symptoms and signs

Skin manifestations are a common presentation of SLE.

The characteristic malar or butterfly rash occurs in 30% to 40% of patients, and may be more common in female patients.[40] [51] This erythematous rash extends from the cheeks over the bridge of the nose, sparing the nasolabial folds. It can be painful and pruritic, usually lasts for a few days, and heals without scarring. Malar rash often recurs after sun exposure. When rash occurs both above and below the neck it is referred to as acute generalized cutaneous lupus rash. Recent onset of photosensitivity is supportive of the diagnosis.



Malar rash: butterfly shape, flat, non-tender erythematosus rash over the cheek and nose

Kumar N et al. BMJ Case Reports. 2013;2013:bcr-2012-008101

a) Photograph of a face with skin rashes sparing the bridge of the nose and malar area. b) Photograph of a face showing asymmetric hyperpigmented, polycylic, and annular scaly plaques with scaling involving pre-auricular area and cheek

Rajasekharan C et al. BMJ Case Reports. 2013;2013:bcr-2012-007886

Other distinct categories of rash include discoid lupus, which presents as erythematous raised patches with adherent keratotic scaling and follicular plugging. Atrophic scarring may occur in older lesions. The latter patterns are less likely to be associated with systemic disease, but many patients are antinuclear antibody (ANA)-positive.

Mouth ulcers, and less frequently nose ulcers, occur in up to 45% of patients. They are usually large and painless, in contrast to herpetic lesions.[52] These ulcers often improve with simple local measures and their course parallels the disease course.

Active systemic disease can lead to diffuse patchy alopecia, which is reversible once disease is controlled. Discoid lesions leave permanent scarring alopecia.

Musculoskeletal symptoms and signs

Musculoskeletal symptoms are common, occurring in the majority of patients at some time during the course of the illness. Determining the distribution and the nature of the symptoms is helpful. A diurnal variation in pain, worse in the mornings with associated stiffness, suggests an underlying inflammatory component. Arthritis tends to be symmetrical and is typically nonerosive. Although uncommon, joint deformity may occur; joint deformity in the absence of erosive disease is referred to as Jaccoud arthritis. Correctable ulnar deviation and joint subluxations in the hands in the absence of radiologic damage are characteristic. Patients with SLE may also develop myositis leading to muscle weakness and pain.

A full history and musculoskeletal examination, looking for tenosynovitis and peripheral joint synovitis, particularly in the hands, should be performed. X-rays of affected joints should be requested. Septic arthritis should always be excluded in a patient presenting with a monoarthritis. The affected joint should

be aspirated and fluid sent for microscopy and culture. Poorly localized proximal limb inflammatory pain with weakness may suggest an associated myositis and, if present, creatinine phosphokinase will be elevated. Diffuse musculoskeletal pain without a distinct diurnal variation may suggest coexisting fibromyalgia; typical tender points should be examined.

Raynaud phenomenon

Recent onset of triphasic color change in both hands and feet in a young woman due to exposure to cold or emotional stress should prompt a search for other features of SLE. The nail folds (for capillary nail fold changes) and peripheral pulses should be examined. The skin over the dorsum of the hands should be checked for sclerodactyly and features of systemic sclerosis or mixed connective tissue disease considered.

Renal symptoms and signs

Renal involvement is present in approximately 50% to 70% of patients, and may be more common in male patients.[40] [53] Lupus nephritis is more common in Hispanic and black patients, and those with more severe disease in other organ systems. Those with antibodies to double-stranded (ds)DNA are more likely to develop glomerulonephritis. Most patients are asymptomatic. Other presentations include hypertension, nephrotic syndrome, or renal failure. Urinalysis may demonstrate the presence of hematuria, casts (red cell, granular, tubular, or mixed), or proteinuria.

Central nervous system symptoms and signs

Major central nervous system involvement in SLE is uncommon.[54] Seizures, cranial nerve abnormalities, and psychiatric illnesses are the most common. Cranial nerve abnormalities may manifest as visual field defects, blindness, papilledema, nystagmus, ptosis, or facial palsy. Myasthenia gravis and multiple sclerosis should be excluded. Psychiatric illnesses include psychosis, depressive disorders, and organic brain syndromes. Cerebral infarcts may occur and are usually related to coexisting positive antiphospholipid antibodies.

Case reports suggest that catatonia may be a manifestation of neuropsychiatric SLE, particularly in the presence of serologies and symptoms indicative of an active lupus flare.[55]

The diagnosis of cerebral involvement in SLE is clinical. Other causes such as sepsis, uremia, malignant hypertension, epilepsy, myasthenia gravis, and multiple sclerosis should be excluded.

Cardiopulmonary symptoms and signs

Cardiovascular manifestations of SLE include pericarditis, myocarditis, endocarditis, arterial and venous thrombosis, and premature atherosclerotic coronary artery disease. The risk of cardiovascular events (myocardial infarction and stroke) is two- to threefold higher in patients with SLE compared with the general population.[56] [57] [58] [59] [60]

Myocarditis should be suspected in patients with tachycardia, arrhythmias, conduction defects, or unexplained cardiomegaly. Nonbacterial Libman-Sacks endocarditis is uncommon.

Pulmonary manifestations of SLE include pleuritis, pleural effusions, diffuse interstitial lung disease, pulmonary hypertension and, rarely, pulmonary hemorrhage.[61] Pulmonary embolism should be excluded in patients with SLE presenting with pleuritic chest pain, dyspnea, and hemoptysis, particularly if antiphospholipid antibodies are positive. Pleural effusions in SLE are usually unilateral and generally exudative. Other causes of a pleural effusion should be excluded.

Shrinking lung syndrome is a rare respiratory manifestation of SLE characterized by dyspnea, chest pain, a raised hemidiaphragm, and a restrictive pattern on pulmonary function tests.[62]

Hematologic symptoms and signs

Anemia, leukopenia, and thrombocytopenia are common hematologic manifestations of SLE.[63] Anemia is usually secondary to chronic disease and improves with control of disease activity. Hemolytic anemia is not common, but can be very severe. Leukopenia is usually due to lymphopenia and to a lesser extent neutropenia. Thrombocytopenia is also frequently seen and other causes should be excluded. The presence of antiphospholipid antibodies increases the risk of venous and arterial thromboses.

Gastrointestinal symptoms and signs

SLE can affect any part of the gastrointestinal tract.[64] Oral ulcers are common.[65] Dysphagia is less common and is due to esophageal hypomotility. Abdominal pain, vomiting, and diarrhea may be caused by lupus peritonitis or mesenteric artery occlusion, but other causes of an acute abdomen should be excluded. Although rare, lupus peritonitis may mimic appendicitis. Pancreatitis may be due to SLE, but it is important to exclude treatment such as azathioprine as the underlying cause. Chronic active hepatitis may occur in SLE.

Serositis

Pleuritis and pericarditis is much more common than peritonitis. In the absence of any other explanation, the diagnosis of SLE should be considered in a patient with anterior chest pain suggestive of pleuritis and pericarditis (especially in at-risk patients such as women of reproductive age). The patient should be asked about mucocutaneous and musculoskeletal features, which, if present, may suggest the diagnosis.

Initial tests

Positive ANA is diagnostic of SLE when it occurs together with the ACR revised criteria for the classification of SLE.[1]

The following tests should be performed in anyone with suspected SLE:

- Complete blood count and clotting screen: a prolongation of the partial thromboplastin time would suggest the presence of lupus anticoagulant and should prompt checking of antiphospholipid antibodies. Antiphospholipid antibodies should also be checked in patients with a history of recurrent spontaneous abortions and thromboses
- Infection screen to include blood and urine cultures should be obtained in febrile patients. Septic arthritis should always be excluded in a patient presenting with a monoarthritis as it needs to be treated expeditiously
- BUN and electrolytes to exclude or confirm possible renal involvement
- Elevated erythrocyte sedimentation rate and CRP are suggestive of active disease, but infection must be excluded
- Urinalysis should be done in all patients suspected of having SLE and regularly in patients with SLE, even in the absence of symptoms. All patients with lupus nephritis have proteinuria
- Autoantibodies for antinuclear factor, dsDNA, and Smith antigen. A positive ANA in itself is not diagnostic as it may be positive in other connective tissue diseases such as rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, thyroid disease, chronic infectious diseases, and inflammatory bowel disease, and in patients treated with certain drugs such as procainamide, hydralazine, isoniazid, and chlorpromazine. ANAs in a low titer also occur in healthy people. One

in 3 will have a positive ANA at the screening dilution of 1:40 and 1 in 20 will have an ANA titer of 1:160.[66] As ANA can be positive in so many conditions, the result of a positive ANA has to be interpreted in the light of the clinical history and symptoms. Rarely, the ANA can be negative in SLE, especially in anti-Ro-antibody-positive lupus (Ro is also known as Sjogren syndrome A or Sjogren antibody). The ACR recommends the immunofluorescence ANA test using human epithelial type 2 (HEp-2) substrate as the gold standard for ANA testing.[67] [68] Anti-dsDNA and anti-Smith antibodies are highly specific for SLE and often are confirmatory of the diagnosis, if present.[69] [70] High titers of anti-dsDNA antibodies are markers of disease activity and high levels predict worse outcome in lupus nephritis.

Subsequent tests

Hematologic

- Coombs test should be ordered if initial blood count shows anemia and features of hemolysis, such as elevated MCV and reticulocyte count.
- Complement levels should be considered but are not necessary to diagnose SLE. They can be used in the setting of significant organ manifestations such as cerebritis or nephritis. Sequential rather than single measurements are necessary to be of value, in order to follow response to treatment or confirm worsening disease.

Immunologic

- Antiphospholipid antibodies should be ordered in patients with a history of venous or arterial thromboses, miscarriages, or in patients with a prolonged activated PTT.
- Skin biopsy is often not necessary to confirm the diagnosis of mucocutaneous manifestations as these are typically diagnosed clinically, but would be performed if diagnosis is in doubt. Skin biopsy of affected areas may show classic immune deposits at the dermal-epidermal junction on immunofluorescence or nonspecific inflammation.

Musculoskeletal

- If there are symptoms and signs of musculoskeletal involvement, x-rays of affected joints should be requested.
- If there is evidence of poorly localized proximal limb inflammatory pain with weakness, creatinine phosphokinase may be done to exclude myositis.

Renal

- 24-hour urine collection for protein or spot urine for protein/creatinine ratio should be performed if the urinalysis is abnormal.
- A renal ultrasound should be performed in patients with abnormal urinary sediment.
- A renal biopsy is the most sensitive and specific test for confirming the diagnosis of lupus nephritis and grading the extent of involvement by the International Society of Nephrology (ISN) and Renal Pathology Society (RPS) classification of lupus nephritis.[5] As renal involvement usually develops in the first few years of illness, blood pressure, urinalysis, and estimated glomerular filtration rate should be monitored. If any are abnormal, specialist opinion with a view to biopsy should be considered. If glomerulonephritis is present, it is classified on the basis of the ISN/RPS system.

Cerebral

- Cerebral manifestations are typically diagnosed clinically. Central nervous system (CNS) lupus can be a diagnostic challenge. Brain MRI may be necessary if the diagnosis is in doubt and will show

small focal areas of increased signal, which could be areas of inflammation. These lesions may resolve with treatment.

- In patients with SLE with progressive cognitive loss, clinical evidence of SLE activity should be sought, and other causes (such as infection, electrolyte disturbance, vitamin or thyroid deficiency, or medication side-effects) need to be excluded.
- Antiribosomal P is significantly associated with CNS involvement and psychosis.[71] [72] Standardization of antiribosomal P assays is required.

Cardiopulmonary

- Patients presenting with cardiopulmonary symptoms should have a chest x-ray and ECG done routinely.[73] Depending on the presenting complaint, echocardiogram, pulmonary function tests, or chest CT may be required. Patients presenting with pleural effusions need pleural aspiration to confirm the cause.

History and exam

Key diagnostic factors

malar (butterfly) rash (common)

- The characteristic malar or butterfly rash occurs in 30% to 40% of patients, and may be more common in female patients.[40] [75]
- Most commonly erythema over the cheeks and bridge of nose, sparing the nasolabial folds.
- Malar rash often recurs after sun exposure. Recent onset of photosensitivity is supportive of the diagnosis.
- 

a) Photograph of a face with skin rashes sparing the bridge of the nose and malar area. b) Photograph of a face showing asymmetric hyperpigmented, polycylic, and annular scaly plaques with scaling involving pre-auricular area and cheek

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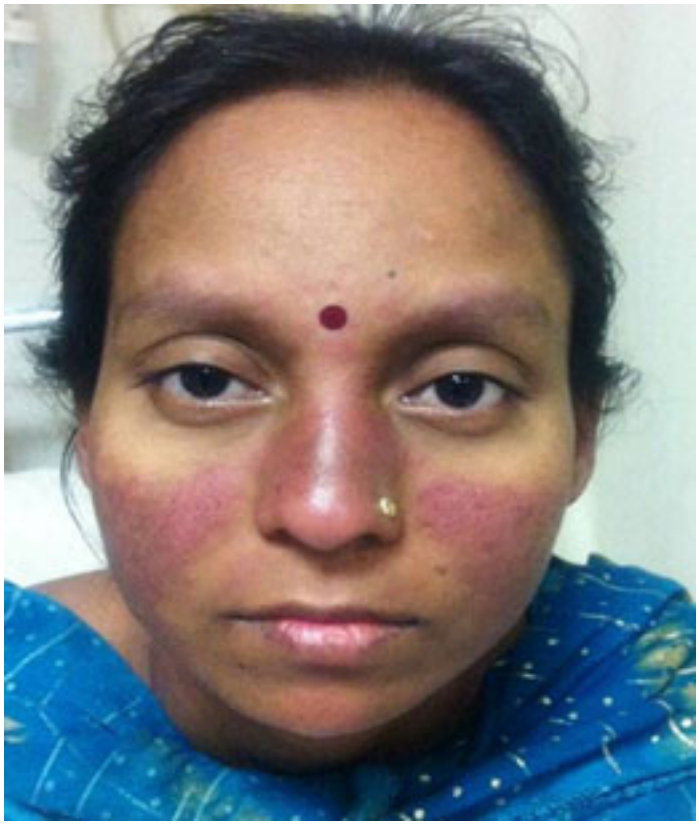

Malar rash: butterfly shape, flat, non-tender erythematosus rash over the cheek and nose

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photosensitive rash (common)

- Rash occurs after sun exposure. It can be painful and pruritic and usually lasts a few days, healing without scarring.

discoid rash (common)

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

Other diagnostic factors

fatigue (common)

- A common complaint in patients with SLE, occurring in 80% to 100% of patients.[48] [49] Absence of other symptoms suggestive of SLE excludes the diagnosis. The occurrence of fatigue is often independent of signs and symptoms in other systems.

weight loss (common)

- Often parallels the course of the illness.
- Vomiting and diarrhea may contribute to weight loss. SLE is associated with an increased risk for cancer, and this should be considered as a potential cause of weight loss.

fever (common)

- Unexplained fever is common and characteristic for SLE.[1] It is thought to represent active disease.
- Elevated C-reactive protein is suggestive of infection rather than underlying disease.
- Exclusion of infection is important before initiating immunosuppressive therapy in a patient with SLE to prevent reactivation or exacerbation of chronic infection.[50]

oral ulcers (common)

- Occur in up to 45% of patients.[52]
- Typically painless but prolonged and recurrent.

alopecia (common)

- Hair thinning and patchy alopecia are an understandable concern in young women with SLE. Parallels the systemic disease course.
- Usually nonscarring.
- Areas of scarring alopecia are more characteristic of chronic discoid lupus.

arthralgia/arthritis (common)

- Arthralgia is common in SLE. Inflammatory joint symptoms occur in >50% of patients.[50] [53] [76]
- The arthritis can be similar to rheumatoid arthritis, although classically nonerosive.
- Monoarthritis of a large joint is unusual in a patient with SLE and should initially prompt the search for another cause such as infection or avascular necrosis.

fibromyalgia (common)

- Poorly localized symmetrical musculoskeletal pain with no diurnal variation.
- Poorly responsive to analgesics/nonsteroidal anti-inflammatory drugs suggests coexisting fibromyalgia; typical tender points should be checked for.

Raynaud phenomenon (common)

- Color changes of the digits induced by cold or emotion. Typical triphasic color change from white to blue to red in fingers and/or toes. Invariably bilateral and occurs in as many as 50% of patients at disease onset, though often predating other features of SLE.[50] [53] It is often less severe than that seen in systemic sclerosis.
- Raynaud phenomenon leading to ulceration is unusual and should prompt consideration of other causes.

chest pain and shortness of breath (common)

- Pleuritis is more common than pericarditis. In a survey of 1000 European patients with SLE, pleuritis and/or pericarditis was noted in 16%.[77] Pleuritis can be either unilateral or bilateral. In a minority, pleural effusions can coexist.
- Other cardiovascular manifestations include myocarditis, endocarditis, venous or arterial thrombosis, and premature atheromatous coronary artery disease.
- Shrinking lung syndrome is a rare manifestation of SLE characterized by shortness of breath, chest pain, a raised hemidiaphragm, and a restrictive pattern on pulmonary function tests.[62]

venous or arterial thrombosis (common)

- The presence of antiphospholipid antibodies increases the risk of venous or arterial thrombosis.[78]

hypertension (common)

- May occur as part of cardiopulmonary manifestations.
- Renal involvement is usually subclinical and usually develops in the first few years of illness. Hypertension may be one of the first signs of lupus nephritis. Blood pressure and urinalysis looking for proteinuria and hematuria should be routinely performed.

signs of nephrosis (e.g., edema) (common)

- Renal involvement is present in approximately 50% to 70% of patients, and may be more common in male patients.[53] [40] Renal involvement is usually subclinical and usually develops in the first few years of illness.
- Blood pressure and urinalysis looking for proteinuria and hematuria should be routinely performed.

lymphadenopathy (common)

- Peripheral lymphadenopathy is more often regional than generalized. The nodes are usually nontender, vary in size from shotty (clusters of small lymph nodes, each a few mm) to 3 to 4 cm, and often are in the cervical and axillary regions.
- Hilar lymphadenopathy is uncommon.
- Patients with lymphadenopathy are more likely to have constitutional manifestations.
- Lymphoma and infectious mononucleosis should be excluded.
- Histology of lymph node biopsies in SLE frequently shows reactive hyperplasia.

abdominal pain, vomiting, or diarrhea (common)

- Occurs as part of gastrointestinal manifestation of SLE. Caused by lupus peritonitis or mesenteric artery occlusion. Peritonitis is rare.

nose ulcers (uncommon)

- Typically painless but prolonged and recurrent.

poorly localized proximal limb inflammatory pain with weakness (uncommon)

- Suggestive of an associated myositis; if present, creatinine phosphokinase will be elevated.

dysrhythmias (e.g., tachycardia), conduction defects, or unexplained cardiomegaly (uncommon)

- Myocarditis should be suspected in these patients.

CNS signs: seizures, cranial nerve abnormalities, cognitive defects, psychosis (uncommon)

- Major central nervous system (CNS) involvement in SLE is uncommon.[54] Other possible causes should be excluded.
- Antiribosomal P is significantly associated with CNS involvement and psychosis.[71] [72] Standardization of antiribosomal P assays is required.
- Investigations in patients with neuropsychiatric symptoms should be similar to that of the general population presenting with the same symptoms.[47]

dysphagia (uncommon)

- Occurs as part of gastrointestinal manifestation of SLE.
- Due to esophageal hypomotility.

Risk factors

Strong

female sex

- The incidence of SLE is higher in women than in men; reported gender ratios range from 2:1 to 15:1.[8] [9] [10]
- The increased frequency of SLE among women has been associated with the effects of estrogen.[6] [13]
- Alopecia, photosensitivity, oral ulcers, arthritis, and malar rash may be more common among female patients.[40]

age >30 years

- Peak age of onset ranges from 30 to 70 years of age in women and between 50 and 70 years in men.[6] [8]

African descent in Europe and US

- The US Centres for Disease Control and Prevention National Lupus Registries found that prevalence was higher in African Americans (230.9 per 100,000 and 26.7 per 100,000 for women and for men, respectively), than in Hispanics (120.7 per 100,000 and 18.0 per 100,000, respectively) or white populations (84.7 per 100,000 and 8.9 per 100,000, respectively).[11]
- Reported incidences in Africa are low (0.3 per 100,000 person-years).[6] This may reflect under-diagnosis due to resource shortage.

drugs

- Clinical and serologic manifestations can occur in patients taking some medications.[25] [41]
- The first reported association was with procainamide, but other commonly implicated drugs include minocycline, terbinafine, sulfasalazine, isoniazid, phenytoin, and carbamazepine.[26] [27] [28] [29] [30] [31] [32] [33]
- Symptoms of drug-induced lupus erythematosus resolve when the offending drug is discontinued.
- Some of the reported associations between drug use and a subsequent diagnosis of SLE may be due to protopathic bias (when a treatment is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed).[41]

Weak

sun exposure

- Exposure to ultraviolet (UV) radiation can exacerbate skin lesions in lupus erythematosus patients (photosensitivity). Sun exposure is the most obvious environmental factor that exacerbates SLE.[42]
- Prospective, methodologically robust studies are required to evaluate the relationship between UV-B and incident SLE.

family history of SLE

- Familial aggregation and higher-than-expected rates of concordance in twin studies suggest that genetic factors are important.[14] [15]
- The heritability of SLE has been estimated to be 43.9%.[16]

tobacco smoking

- Smoking increases the risk of SLE.[43] [44]
- It has also been shown to worsen the course and outcome of disease, and is associated with cumulative chronic damage.[44] [45] [46]

Tests

1st test to order

Test	Result
complete blood count and differential • Should be ordered in anyone suspected of having SLE. • Leukopenia is usually caused by lymphopenia rather than neutropenia. • Drugs and infection should be excluded as a cause of the cytopenias.	**anemia, leukopenia, thrombocytopenia; rarely pancytopenia**
activated partial thromboplastin time • To be considered in anyone suspected of having SLE.	**may be prolonged in patients with antiphospholipid antibodies**
BUN and electrolytes • Ordered in anyone suspected of having SLE. • Identifies those patients with SLE who have renal manifestations.	**elevated BUN and creatinine**
erythrocyte sedimentation rate and C-reactive protein • Nonspecific markers that may be elevated due to an acute phase response from any cause. • Patients with SLE have systemic inflammation. Erythrocyte sedimentation rate (ESR) may be elevated due to high levels of immunoglobulins. • Elevated ESR and C-reactive protein should prompt a search for infection but could also be due to active disease.	**elevated (nonspecific)**
antinuclear antibodies, double-stranded (ds)DNA, Smith antigen • Done in anyone suspected of having SLE. • Antinuclear antibody (ANA) is positive in virtually all patients with SLE.[79] Clinically relevant ANAs are IgG antibodies. • Currently the most sensitive test for confirming the diagnosis of SLE when accompanied by typical clinical findings. • A positive ANA in itself is not diagnostic as it may be positive in other connective tissue diseases such as rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, thyroid disease, chronic infectious diseases, and inflammatory bowel disease, and in patients treated with certain drugs such as procainamide, hydralazine, isoniazid, and chlorpromazine. • ANAs in a low titer also occur in healthy people: 1 in 3 will have a positive ANA at the screening dilution of 1:40 and 1 in 20 will have an ANA titer of 1:160.[66] As ANA can be positive in so many conditions, the result of a positive ANA has to be interpreted in the light of the clinical history and symptoms. • Rarely, the ANA can be negative in SLE, especially in anti-Ro-antibody-positive lupus (Ro is also known as Sjogren syndrome A or Sjogren antibody). The American College of Rheumatology recommends the immunofluorescence ANA test using human epithelial type 2 (HEp-2) substrate as the gold standard for ANA testing.[67] [68] Anti-dsDNA and anti-Smith antibodies are highly specific for SLE and often are confirmatory of the diagnosis, if present.[69] [70] High titers of anti-dsDNA antibodies are markers of disease activity and high levels are predictors of worse outcome in lupus nephritis.	**positive**

Test	Result
urinalysis • To assess renal involvement and should be done in anyone suspected of having SLE.	**hematuria, casts (red cell, granular, tubular, or mixed), or proteinuria**
chest x-ray • All patients presenting with cardiopulmonary symptoms should have a CXR performed.	**pleural effusion, infiltrates, cardiomegaly**
ECG • All patients presenting with cardiopulmonary symptoms should have an ECG performed.[73]	**may exclude other causes of chest pain**

Other tests to consider

Test	Result
blood and urine cultures • Performed in febrile patients.	**may exclude infection**
antiphospholipid antibodies • Antiphospholipid antibodies should be ordered in patients with a history of venous or arterial thromboses, miscarriages, or in patients with a prolonged activated partial thromboplastin time.	**positive**
Coombs test • Ordered if initial blood count shows an anemia as well as features of hemolysis such as elevated MCV and reticulocyte count.	**positive**
24-hour urine collection for protein or spot urine for protein/creatinine ratio • Performed if urinalysis is abnormal.	**proteinuria**
complement levels • Complement levels should be considered but are not necessary to diagnose SLE. They can be used if there are significant organ manifestations such as cerebritis or nephritis. Sequential rather than single measurements are necessary to be of value, in order to follow response to treatment or confirm worsening disease. • Low C4 levels are common as they may be due to C4 null alleles (genetically low levels), and thus C4 levels are not always helpful in monitoring the disease. • Active disease may result in low C3 levels, but increased synthesis due to an acute phase response may confound interpretation. Although activation products can be measured, they are not frequently available.	**complement consumption**
creatine phosphokinase • Performed in patients with myalgia and weakness. If elevated, an underlying inflammatory myositis should be considered.	**may be elevated**
plain x-rays of affected joint(s) • Done in patients suspected of having SLE with symptoms of arthralgia or arthritis.	**inflammation, nonerosive arthritis**
renal ultrasound • Done in patients with SLE and renal involvement: for example, patients with abnormal urinary sediment on urinalysis.	**to exclude other causes of renal impairment**
chest computed tomography • Done in patients with SLE complaining of respiratory symptoms and signs.	**lung fibrosis, effusions**
pulmonary function tests • Done in patients with SLE complaining of respiratory symptoms and signs indicating fibrosis.	**restrictive pattern**
pleural aspiration • Performed to identify cause of pleural effusion.	**exudate**

Test	Result
brain magnetic resonance imaging • May be done in patients with suspected cerebral lupus, although central nervous system involvement is typically diagnosed clinically.	**white matter changes**
echocardiography • Done in patients with symptoms and signs of pericarditis or pulmonary hypertension.	**pericarditis, pericardial effusion, pulmonary hypertension**
skin biopsy • Often not necessary to confirm the diagnosis of mucocutaneous manifestations as these are typically diagnosed clinically. Skin biopsy should be done if the diagnosis is in doubt.	**immune deposits at the dermal-epidermal junction on immunofluorescence or nonspecific inflammation**
renal biopsy • A renal biopsy is the most sensitive and specific test for diagnosis of lupus nephritis. As it is invasive and not without risks, patients with renal involvement should be assessed by a nephrologist.	**immune deposits, mesangial hypercellularity; focal, segmental, or global glomerulonephritis**
thyroid-stimulating hormone • Thyroid-stimulating hormone is elevated in primary hypothyroidism.	**normal level usually excludes hypothyroidism**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Rheumatoid arthritis	• May be difficult to differentiate clinically. • Patients with SLE frequently present with an inflammatory arthritis with a similar pattern to rheumatoid arthritis, although it tends to be less symmetrical.	• Joint x-rays demonstrate symmetrical, erosive arthritis.
Antiphospholipid syndrome	• Characterized by the occurrence of venous or arterial thrombosis or recurrent fetal loss in the presence of antiphospholipid antibodies.	• Antiphospholipid antibodies: anticardiolipin antibodies IgG or IgM present in moderate or high levels on ≥2 occasions at least 6 weeks apart and lupus anticoagulant detected on ≥2 occasions at least 6 weeks apart. These antibodies may also be positive in SLE. • About 10% of patients with antiphospholipid syndrome are b2-glycoprotein positive.[80] • Venereal Disease Research Laboratory (VDRL) test: false-positive result.
Systemic sclerosis	• Raynaud phenomenon is present in almost all patients with systemic sclerosis, being the initial symptom in about 70% of patients. • Patients with SLE often have Raynaud phenomenon as well, but these tend not to ulcerate compared with patients with systemic sclerosis. • Patients with systemic sclerosis have characteristic sclerodactyly and calcinosis, not present in SLE.	• Autoantibodies: positive anti-centromere antibodies (limited cutaneous systemic sclerosis) or anti-topoisomerase 1 (Scl-70) antibodies (diffuse cutaneous systemic sclerosis).
Mixed connective tissue disease	• Mixed connective tissue disease (MCTD) is characterized by a combination of manifestations similar to those in SLE, systemic sclerosis, and myositis. Difficult to differentiate clinically.	• Autoantibodies: positive anti-RNP antibodies are specific to MCTD. • Patients with MCTD tend to lack other antibodies such as anti-Sm, anti-Ro, anti-La, and anti-dsDNA.

Condition	Differentiating signs / symptoms	Differentiating tests
Adult Still disease	• A variant of juvenile rheumatoid arthritis characterized by seronegative chronic polyarthritis in association with a systemic inflammatory illness, which manifests as symptoms similar to those of SLE. • The fever in adult Still disease usually occurs once or twice daily with marked temperature elevation and normal temperature in between. • The rash is often only seen during febrile periods and is a salmon-colored macular or maculopapular nonpruritic lesion.	• Elevated ferritin has been reported in most patients. Ferritin should therefore be checked in patients presenting with such symptoms and, if elevated, lead to a suspicion of adult Still disease. • Joint symptoms are similar to rheumatoid arthritis and joint erosions and fusion on x-ray may occur, unlike in SLE.
Lyme disease	• May be difficult to distinguish clinically. • History of possible erythema migrans or exposure to ticks.	• Lyme-specific IgM and IgG are positive. • Although the presence of antinuclear antibody is common, the presence of dsDNA and Smith antibodies are not.
HIV	• May be difficult to distinguish clinically. • History of exposure to risk factors for HIV.	• Serum HIV enzyme-linked immunosorbent assay test is positive. • Although the presence of antinuclear antibody is common, the presence of dsDNA and Smith antibodies are not.
Cytomegalovirus	• May be difficult to distinguish clinically. • May be asymptomatic.	• Cytomegalovirus serology is positive for infection. • Although the presence of antinuclear antibody is common, the presence of dsDNA and Smith antibodies is not.
Infectious mononucleosis	• May be difficult to distinguish clinically.	• Positive agglutination test (e.g., monospot). • Although the presence of antinuclear antibody is common, the presence of dsDNA and Smith antibodies is not.

Condition	Differentiating signs / symptoms	Differentiating tests
Hematologic malignancy	• SLE may be difficult to distinguish clinically from hematologic malignancy.	• Bone marrow, other histology or imaging tests may distinguish the diagnosis. • Autoantibodies will be negative.
Glomerulonephritis	• Difficult to differentiate clinically if no other symptoms or signs associated with SLE are present (e.g., Raynaud phenomenon, rash).	• Antibodies for dsDNA may be positive if SLE is the cause. • Renal biopsy may aid in diagnosis.
Chronic fatigue syndrome	• No other signs that are typically associated with SLE (e.g., Raynaud phenomenon, rash) will be present	• Autoantibodies will be negative.
Generalized tonic-clonic seizures	• May be difficult to differentiate clinically as seizures can be a feature of SLE. However, no other signs that are typically associated with SLE (e.g., Raynaud phenomenon, rash) will be present.	• EEG will demonstrate epileptiform activity. • Brain MRI may demonstrate a lesion. • Autoantibodies will be negative in epilepsy.
Fibromyalgia	• Poorly localized symmetrical musculoskeletal pain with no diurnal variation. • Poorly responsive to analgesics/nonsteroidal anti-inflammatory drugs. • May coexist with SLE. • Positive typical tender points.	• Diagnosis is typically clinical. • Autoantibodies will be negative.
Depression	• Typically no systemic manifestations (e.g., rash) unless coexists with SLE.	• Diagnosis is typically clinical. • Autoantibodies will be negative.
Septic arthritis	• May be difficult to differentiate clinically if patient presents with monoarthritis and no other features of SLE.	• Joint aspiration or synovial biopsy yields positive culture.

Criteria

2019 European League Against Rheumatism/American College of Rheumatology classification system[1]

Entry criterion

- Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)
- If absent, do not classify as SLE; if present, apply additive criteria

Additive criteria

- Additive criterion should not be counted if there is a more likely explanation than SLE
- Occurrence of a criterion on at least one occasion is sufficient
- SLE classification requires at least one clinical criterion and ≥10 points
- Criteria need not occur simultaneously
- Within each domain, only the highest criterion is counted toward the score*

Clinical domains and criteria

Constitutional

- Fever, 2 points

Hematologic

- Leukopenia, 3 points
- Thrombocytopenia, 4 points
- Autoimmune hemolysis, 4 points

Neuropsychiatric

- Delirium, 2 points
- Psychosis, 3 points
- Seizure, 5 points

Mucocutaneous

- Nonscarring alopecia, 2 points
- Oral ulcers, 2 points
- Subacute cutaneous OR discoid lupus, 4 points
- Acute cutaneous lupus, 6 points

Serosal

- Pleural or pericardial effusion, 5 points
- Acute pericarditis, 6 points

Musculoskeletal

- Joint involvement, 6 points

Renal

- Proteinuria >0.5 g/24 hours, 4 points
- Renal biopsy class II or V lupus nephritis, 8 points
- Renal biopsy class III or IV lupus nephritis, 10 points

Immunology domains and criteria

Antiphospholipid antibodies

- Anticardiolipin antibodies OR anti-beta2-glycoprotein 1 antibodies OR lupus anticoagulant, 2 points

Complement proteins

- Low C3 OR low C4, 3 points
- Low C3 AND low C4, 4 points

SLE-specific antibodies

- Anti-double-stranded (ds)DNA antibody** OR anti-Smith antibody, 6 points

Total score

Scores of 10 or more are classified as systemic lupus erythematosus if the entry criterion has been fulfilled.

* Additional criteria items within the same domain will not be counted.

** In an assay with ≥90% specificity against relevant disease controls.

1997 update of the 1982 American College of Rheumatology revised criteria for the classification of SLE[2] [3]

These criteria were initially developed to identify patients for clinical studies and were based on a white population. Any ≥4 of the 11 criteria are required to classify a patient as having SLE. These criteria can be present serially or simultaneously during any interval of observation.

1. Malar rash
    - Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. Discoid rash
    - Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3. Photosensitivity
    - Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers
    - Oral or nasopharyngeal ulceration, usually painless, observed by physician.
5. Arthritis
    - Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion.
6. Serositis (one of the following):
    - Pleuritis: convincing history of pleuritic pain, pleural rubs on auscultation, or evidence of pleural effusion
    - Pericarditis: documented by ECG, pericardial rub, or evidence of pericardial effusion.
7. Renal disorder (one of the following):
    - Persistent proteinuria >0.5 g/day or >3+ if quantification not performed
    - Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed.
8. Neurologic disorder (one of the following):
    - Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
    - Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance).
9. Hematologic disorder (one of the following):

- Hemolytic anemia: with reticulocytes
- Leukopenia: <4000/mm³ on ≥2 occasions
- Lymphopenia: <1500/mm³ on ≥2 occasions
- Thrombocytopenia: <100,000/mm³ in the absence of offending drugs.

10. Immunologic disorder (one of the following):

- Anti-DNA: presence of antibody to native DNA in abnormal titer
- Anti-Smith: presence of antibody to Smith nuclear antigen
- Positive findings of antiphospholipid antibodies based on:
  - An abnormal serum level of IgG or IgM anticardiolipin antibodies
  - Positive test result for lupus anticoagulant using a standard method
  - A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.

11. Antinuclear antibody (ANA)

- An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome.

2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus[4]

The SLICC criteria for SLE classification requires:

1. Fulfillment of at least 4 criteria, with at least one clinical criterion AND one immunologic criterion

OR

2. Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Clinical criteria:

- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers: palate
- Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
- Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and 30 minutes or more of morning stiffness
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leukopenia (<4000/mm³ at least once)
- Thrombocytopenia (<100,000/mm³) at least once.

Immunologic criteria:

- ANA above laboratory reference range
- Anti-dsDNA above laboratory reference range, except enzyme-linked immunosorbent assay: twice above laboratory reference range
- Anti-Smith

- Antiphospholipid antibody: any of the following
- Low complement
- Direct Coombs test in the absence of hemolytic anemia.

Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices[5]

- Class I: minimal mesangial lupus nephritis
- Class II: mesangial proliferative lupus nephritis
- Class III: focal lupus nephritis
- Class III (A): active lesions - focal proliferative lupus nephritis
- Class III (A/C):
    - Active and chronic lesions: focal proliferative and sclerosing lupus nephritis class III (C)
    - Chronic inactive lesions: focal sclerosing lupus nephritis
- Class IV: diffuse lupus nephritis
- Class V: membranous lupus nephritis
- Class VI: advanced sclerosis lupus nephritis.

Approach

The goals of treatment for patients with SLE are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, improve quality of life, and educate patients about their role in disease management.[83] [84]

Treatment should target complete remission (the absence of clinical activity with no use of corticosteroids), but this is rarely achieved.[85] Therefore, low disease activity and prevention of flares in all organ systems may be the aim. Low disease activity is considered to be Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≤3 on antimalarials, or alternatively SLEDAI ≤4, physician global assessment (PGA) ≤1 with ≤7.5 mg of prednisone, and well-tolerated immunosuppressive agents.

SLE is a multisystem disease and certain components/complications of the disease (e.g., pleural effusion, pulmonary hypertension, and peritonitis) are managed by other specialists in addition to routine rheumatology care.

Patient education

Patient education involves encouraging the patient to take responsibility for their disease management. Guiding patients to validated resources is an important part of the treatment process.

- [Lupus Foundation of America] (https://www.lupus.org)
- [NIH: systemic lupus erythematosus (lupus)] (https://www.niams.nih.gov/health-topics/lupus)
- [CDC: systemic lupus erythematosus (SLE)] (https://www.cdc.gov/lupus/facts/detailed.html)

Nonpharmacologic treatment

Potential nonpharmacologic interventions for SLE include sun protection, diet and nutrition, exercise, psychological treatment, and smoking cessation.

Sun protection

Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

Diet and nutrition

No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

SLE is associated with inadequate levels of serum vitamin D compared with the general population.[89] [90] [91] In patients with SLE, vitamin D supplements reduce disease activity; increase serum levels; and improve levels of inflammatory markers, fatigue, and endothelial function.[91] [92] [93]

Some evidence suggests omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

Exercise

Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

Psychological intervention

SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT, as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

Smoking cessation

Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

Pharmacologic treatment

Common pharmacologic treatment for SLE includes nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial therapy, corticosteroids, immunosuppressive agents, and biologic agents.

NSAIDs

NSAIDs are frequently used as a first-line measure in SLE to control joint stiffness as well as musculoskeletal and serosal pain. Naproxen may be the preferred first-line agent owing to the rare occurrence of aseptic meningitis with ibuprofen.[101] [102] [103]

Patients who require an anti-inflammatory and who are at high risk of gastrointestinal ulceration should be given a cyclo-oxygenase-2 (COX-2) inhibitor (e.g., celecoxib) if they are at low cardiovascular risk.

Blood pressure should be monitored and NSAIDs should be avoided in patients with hypertension or renal disease.

If long-term NSAID therapy is indicated, *Helicobacter pylori* eradication and the need for gastroprotection should be considered.

Hydroxychloroquine

Hydroxychloroquine is recommended for all patients with SLE (unless contraindicated).[85]

The beneficial effects of hydroxychloroquine in SLE include the reduction of constitutional symptoms, and reduced musculoskeletal and mucocutaneous manifestations.[104] Guidance recommends that patients who are in long-standing remission may lower their dose, although no studies have formally addressed this strategy.[85]

Concerns exist regarding the development of retinal toxicity with hydroxychloroquine therapy.[105] [106] Risk factors include duration of treatment, dose, chronic kidney disease, and preexisting retinal or macular disease.[106] Retrospective case-control study data suggest that risk of toxic retinopathy is low for doses below 5.0 mg/kg of real body weight for up to 10 years.[105]

Ophthalmologic screening (by visual field exam and/or spectral domain-optical coherence tomography) is recommended at baseline, after 5 years, and yearly thereafter in the absence of risk factors for retinal toxicity.[85]

Corticosteroids

Pulse doses of intravenous methylprednisolone are recommended to provide immediate therapeutic effect in SLE and enable the use of a lower starting dose of oral corticosteroid.[85]

The recommended dose and route of administration depends on the type and severity of organ involvement. For chronic maintenance treatment, the dose of oral corticosteroids should be minimized to <7.5 mg/day and, when possible, withdrawn.[85]

The long-term adverse effects of corticosteroid therapy are well documented, and patients should be counseled regarding risk of hypertension and atherosclerotic disease, hyperglycemia, potential skin changes, infection, mood disorders, disorders of bone and muscle (e.g., osteoporosis, osteonecrosis, myopathy), and ophthalmologic effects (e.g., cataracts, increased ocular pressure, exophthalmos). Caution is advised with corticosteroid use in patients with upper gastrointestinal symptoms, especially if also taking NSAIDs. The lowest possible dose to control symptoms should be used for the shortest period of time.

Immunosuppressive agents

The addition of immunosuppressive agents (such as methotrexate, azathioprine, or mycophenolate) should be considered for the treatment of patients:[85]

- with organ-threatening disease
- not responding to hydroxychloroquine (alone or in combination with corticosteroid)
- unable to reduce the corticosteroid dose below the acceptable dose for chronic use.

Early initiation of immunosuppressive agents can expedite the tapering/discontinuation of corticosteroids.[85]

The choice of agent depends on prevailing disease manifestation(s) of SLE, the patient's age, childbearing potential, and safety concerns.[85]

Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as rescue therapy in patients not responding to other immunosuppressive agents.[85]

Biologic agents

B-cell targeting agents such as belimumab and rituximab are beneficial for treating patients with SLE who are refractory to other agents.[107] [108] [109] [110]

Belimumab should be considered as an add-on treatment for patients who have an inadequate response to combination treatment with hydroxychloroquine and corticosteroids with or without immunosuppressive

agents (where inadequate response constitutes residual disease activity not allowing tapering of corticosteroids and/or frequent relapses).[85]

One Cochrane review concluded that there is moderate- to high-quality evidence that belimumab is associated with clinically meaningful benefit for patients with SLE at 52 weeks compared with placebo.[111] Patients receiving the approved dose were found to have at lease at least a 4-point reduction in SELENA-SLEDAI score.[111]

Belimumab significantly reduced organ damage progression compared with standard care in a long-term study (5-year analysis) of patients with SLE.[112]

Rituximab can be considered for patients with organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents.[85]

Other treatments

Other pharmacologic treatments for SLE include dapsone, thalidomide, retinoids, and intravenous immune globulin, depending on clinical circumstances.[85]

Constitutional symptoms

Fatigue is the most common constitutional symptom associated with SLE, occurring in 80% to 100% of patients, but it does not correlate with disease activity.[48] [49] It is important to determine whether there is any evidence of anemia, renal impairment, hypothyroidism, depression, interrupted sleep pattern, or deconditioning and treat each symptom accordingly.[113] [114] [115] Anemia is usually secondary to chronic disease and improves with controlling disease activity.

Fever can be a manifestation of active disease, infection, or drug reaction.[77] [116] Fever due to SLE often resolves with an NSAID or acetaminophen. Persisting fever, despite treatment with these agents, should raise suspicions of an infectious or drug-related etiology.

Joint manifestations and serositis

Hydroxychloroquine can be used in combination with NSAIDs and/or corticosteroids if required to treat arthritis or arthralgia.[117] [118]

If an NSAID is required to control joint stiffness, naproxen may be the preferred first-line agent owing to the rare occurrence of aseptic meningitis with ibuprofen.[101] [102] [103] Patients at high risk of gastrointestinal ulceration should be given a COX-2 inhibitor (e.g., celecoxib) if they are at low cardiovascular risk. If long-term NSAID therapy is indicated, *Helicobacter pylori* eradication and the need for gastroprotection should be considered.

Corticosteroids may be used when NSAIDs and hydroxychloroquine are inadequate. The recommended dose and route of administration of corticosteroids depends on the type and severity of organ involvement.[85]

Additional treatment for joint manifestations and serositis

Early initiation of immunosuppressive agents such as methotrexate or azathioprine can expedite the tapering/discontinuation of corticosteroids.[85]

Methotrexate can be a helpful addition in patients taking oral corticosteroids for arthritis/arthralgia.[119] Patients taking methotrexate should have regular hematologic and liver function testing. Methotrexate use may increase the risk of infection. Abnormal hematologic and/or liver function results may necessitate reduction in prescribed dose.[119]

Belimumab should be considered as an add-on treatment for patients who have an inadequate response to combination treatment with hydroxychloroquine and corticosteroids with or without immunosuppressive agents (where inadequate response constitutes residual disease activity not allowing tapering of corticosteroids and/or frequent relapses).[85]

Rituximab can be considered for patients with organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents.[85]

Mucocutaneous manifestations

For patients with mucocutaneous manifestations, effective protection from ultraviolet exposure with broad-spectrum sunscreens and smoking cessation are strongly recommended.[85]

A thorough oral care regime is recommended for all symptomatic patients.[120] Mouthwashes (e.g., chlorhexidine), basic oral hygiene, and regular attendance at a dental practitioner are helpful in the treatment of mouth ulceration.

Lidocaine ointment may be beneficial for the management of pain secondary to major oral aphthae.[121]

Artificial saliva preparations may be required for those with dry mouth.[120]

Hypromellose eye drops are recommended for dry eyes.

Pharmacologic treatment for mucocutaneous manifestations

First-line treatment of skin disease in SLE includes topical agents (e.g., corticosteroids, calcineurin inhibitors), and oral antimalarials (e.g., hydroxychloroquine) with or without systemic corticosteroids (starting dose dependent on the severity of skin involvement).[85]

One Cochrane review found evidence to support the use of hydroxychloroquine (or chloroquine) and methotrexate for treating cutaneous SLE, but for most key outcomes this was of low or moderate quality.[122] More studies are being evaluated and may change the conclusions of this review.

Topical corticosteroids of different potencies may be used in combination depending on the patient's symptoms. Potent corticosteroids (e.g., betamethasone valerate 0.1%) and very potent corticosteroids (e.g., clobetasol propionate 0.05%) are often used to treat the trunk and limbs including the hands, as well as the scalp. Moderate-potency corticosteroids (e.g., triamcinolone acetonide 0.1% or betamethasone valerate 0.025%) are used in areas more prone to atrophy such as the face and neck. Mild-potency corticosteroids (e.g., hydrocortisone 1%) are typically reserved for the eyelids, although may prove insufficient. Scalp involvement may be treated with foam or lotion formulations.

Additional treatment for refractory mucocutaneous manifestations

Methotrexate, retinoid (e.g., acitretin), dapsone, or mycophenolate can be added for patients who do not respond to first-line treatment (approximately 40%) or who require high-dose corticosteroid.[85]

Belimumab and rituximab also have demonstrated efficacy in mucocutaneous manifestations of SLE, although rituximab may be less efficacious in chronic forms of skin lupus.[85]

Thalidomide should be considered only as a rescue therapy for patients who have failed multiple previous agents due to its strict contraindication in pregnancy, the risk for irreversible polyneuropathy, and the frequent relapses on drug discontinuation.[85]

Lupus nephritis

For renal manifestations of SLE, induction therapy is required to achieve complete or partial response, followed by immunosuppression to maintain the response. An early significant drop in proteinuria (to ≤1 g/day at 6 months or ≤0.8 g/day at 12 months) is a predictor of favorable long-term renal outcome.[85]

Induction therapy for lupus nephritis

Mycophenolate or low-dose intravenous cyclophosphamide are recommended as initial induction treatment, as they have the best efficacy/toxicity ratio.[85] [123] [124] [Evidence C] Therapeutic regimens considered for patients at high risk for renal failure are similar, but high-dose intravenous cyclophosphamide can be used.[85]

One systematic review and meta-analysis found that mycophenolate significantly increased the level of serum complement C3 compared with cyclophosphamide.[125] Mycophenolate was also superior to cyclophosphamide with respect to secondary end points of complete remission and adverse reactions.

Corticosteroids are also given as part of the induction regimen in addition to background treatment with hydroxychloroquine.[82] [126] Continued hydroxychloroquine is associated with increased remission rates in patients initially treated with mycophenolate for lupus nephritis.[127]

Belimumab is approved for the treatment of adults with lupus nephritis. In a randomized double-blind trial, significantly more patients who received belimumab plus standard therapy had a renal response (43% vs. 32%; defined as ratio of urinary protein to creatinine of 0.7 or less, an estimated glomerular filtration rate that was no worse than 20% below the pre-flare value or at least 60 mL/minute/1.73 m², and no use of rescue therapy for treatment failure) compared with standard therapy alone.[128]

Cyclophosphamide should be given with adequate fluid and mesna (a uroprotective agent) as there is a risk of uro-epithelial toxicity (e.g., hemorrhagic cystitis). Young women should be advised about the risks of amenorrhea or premature ovarian failure with cyclophosphamide; gynecologic referral may be required for further in-depth discussion. Male patients should also be counseled regarding possible risk of infertility. The risk of amenorrhea is lower with mycophenolate, although there are concerns about congenital malformations if it is given during pregnancy.

Second-line treatment for renal manifestations

Calcineurin inhibitors (e.g., cyclosporine) may be considered as second-line agents for induction therapy in membranous lupus nephritis, podocytopathy, or proliferative disease with refractory nephrotic syndrome despite standard-of-care within 3 to 6 months.[85] Calcineurin inhibitors may be used alone, or in combination with mycophenolate, to treat proliferative lupus nephritis.[129] [130] [131] [132] [133] [134]

For patients with refractory nephrotic syndrome, tacrolimus may be used alone or in combination with mycophenolate, as this combination is effective in disease refractory to standard therapy.[85] [135]

Monitoring serum creatinine and blood levels of patients being treated with calcineurin inhibitors is essential to avoid chronic drug toxicity.[85]

Maintenance therapy for lupus nephritis

Once a patient has attained complete or partial response, immunosuppression is continued to maintain the response.

First-line maintenance therapy for renal manifestations

For maintenance therapy, mycophenolate or azathioprine should be used in combination with corticosteroids.[85] Either treatment can be used for maintenance therapy after induction with cyclophosphamide or mycophenolate, and is more effective in preserving renal function than corticosteroids alone.[136]

Second-line maintenance therapy for renal manifestations

Calcineurin inhibitors may be considered as second-line agents for maintenance therapy in membranous lupus nephritis, podocytopathy, or proliferative disease with refractory nephrotic syndrome despite standard-of-care within 3 to 6 months.[85]

One systematic review and meta-analysis of the effect of calcineurin inhibitors for the induction and maintenance treatment of lupus nephritis found that calcineurin inhibitor treatment during the maintenance period was as effective as azathioprine treatment, with a much lower risk of adverse effects.[131]

Monitoring serum creatinine and blood levels of patients being treated with calcineurin inhibitors to avoid chronic drug toxicity is essential.[85]

Neuropsychiatric manifestations

Attribution of neuropsychiatric manifestations to SLE (by neuroimaging, investigation of cerebrospinal fluid, and consideration of risk factors), as opposed to non SLE, is essential.[85]

First-line treatment for neuropsychiatric manifestations

Treatment of SLE-related neuropsychiatric disease includes immunosuppressive agents and corticosteroids for manifestations considered to reflect an inflammatory process, and antiplatelet agents/anticoagulants for atherothrombotic/antiphospholipid-related manifestations.[85] The choice of immunosuppressive agent (e.g., azathioprine, mycophenolate, methotrexate) will depend on individual cases, as the neuropsychiatric manifestations can be varied.

Distinction between the two pathophysiologic processes may be difficult in practice. The two processes could coexist in the same patient. Combination of an immunosuppressive agent and antiplatelet agent/anticoagulant therapy may be considered in these patients.[85]

Patients with SLE with cerebrovascular disease should be managed like the general population in the acute phase; in addition to controlling extra-central nervous system lupus activity, immunosuppressive therapy may be considered in the absence of antiphospholipid antibodies and other atherosclerotic risk factors or in recurrent cerebrovascular events.[85]

In this context, neuroimaging and/or cerebrospinal fluid studies may provide additional supporting evidence for immunosuppressive therapy.[85]

Ancillary therapies for neuropsychiatric manifestations

Targeted symptomatic therapy is indicated according to the type of manifestation.[85]

- Antipsychotics can be used if required for psychotic symptoms in central nervous system lupus.
- Antidepressants may be helpful in certain cases. Treatment regimes as per patients without SLE.
- Migraine treatments may be helpful in certain cases. Treatment regimes as per patients without SLE.
- Anticonvulsants may be used (e.g., for peripheral neuropathy).

Alternative or additional treatment for refractory neuropsychiatric manifestations

Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as rescue therapy in patients not responding to other immunosuppressive agents.[85] Rituximab can be considered for patients with organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents. Evidence of benefit in severe refractory neuropsychiatric SLE is limited to case reports.

Intravenous immune globulin (IVIG) may be used as adjunctive therapy when initial treatment is inadequate, but the quality of evidence supporting its use is poor (small cohort studies).[137] IVIG can be effective in the treatment of SLE-associated peripheral neuropathies.

Plasmapheresis may also be considered as an adjunctive treatment.[137] The aim of the treatment is to remove circulating autoantibodies. Recommended if there are clinical and investigative findings consistent with cerebral vasculitis, and may be used when earlier treatments are inadequate.[137]

Hematologic manifestations

Hematologic manifestations that require anti-inflammatory/immunosuppressive treatment in patients with SLE include thrombocytopenia and autoimmune hemolytic anemia.[85]

Evidence suggests that patients with SLE and thrombocytopenia have an increased risk of mortality and end-organ damage.[138]

First-line treatment for hematologic manifestations

Treatment of significant lupus thrombocytopenia (platelet count below 30,000/mm^3) and autoimmune hemolytic anemia consists of moderate/high doses of corticosteroids in combination with an immunosuppressive agent (e.g., azathioprine, mycophenolate, cyclosporine) as a corticosteroid-sparing agent.

Initial therapy with pulse dose of intravenous methylprednisolone is encouraged.[85]

Additional treatment for hematologic manifestations

IVIG may be considered in the acute phase, in cases of inadequate response to high-dose corticosteroids or to avoid corticosteroid-related infectious complications.[85]

Alternative treatment for refractory for hematologic manifestations

Rituximab or cyclophosphamide should be considered in patients with no response to corticosteroids or patients who have relapsed.[85]

Thrombopoietin agonists or splenectomy should be reserved as last options.[85]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
joint symptoms and serositis		
	1st	hydroxychloroquine
	plus	lifestyle changes and psychological therapies
	adjunct	nonsteroidal anti-inflammatory drug
	adjunct	corticosteroid
	adjunct	immunosuppressant
	adjunct	belimumab or rituximab
mucocutaneous disease		
	1st	hydroxychloroquine
	plus	topical corticosteroid or calcineurin inhibitor
	plus	lifestyle changes, supportive care, and psychological therapies
	adjunct	corticosteroid
	adjunct	immunosuppressant or dapsone or a retinoid
	adjunct	belimumab or rituximab
	adjunct	thalidomide
lupus nephritis		
	1st	induction therapy
	plus	hydroxychloroquine
	plus	corticosteroid
	plus	lifestyle changes and psychological therapies
	plus	maintenance therapy
	adjunct	belimumab or rituximab
neuropsychiatric lupus		
■ inflammatory only	1st	immunosuppressant
	plus	corticosteroid

Ongoing (summary)

	plus	lifestyle changes and psychological therapies
	adjunct	rituximab
	adjunct	intravenous immune globulin (IVIG)
	adjunct	plasmapheresis
	adjunct	targeted symptomatic pharmacotherapy
atherothrombotic/ antiphospholipid-related manifestations only	1st	antiplatelet agent or anticoagulation
	plus	lifestyle changes and psychological therapies
	adjunct	immunosuppressant
	adjunct	intravenous immune globulin (IVIG)
	adjunct	plasmapheresis
	adjunct	targeted symptomatic pharmacotherapy
inflammatory and atherothrombotic/ antiphospholipid-related manifestations	1st	immunosuppressant
	plus	antiplatelet agent or anticoagulation
	plus	lifestyle changes and psychological therapies
	adjunct	rituximab
	adjunct	intravenous immune globulin (IVIG)
	adjunct	plasmapheresis
	adjunct	targeted symptomatic pharmacotherapy
hematologic manifestations		
	1st	immunosuppressant
	plus	corticosteroid
	plus	lifestyle changes and psychological therapies
	adjunct	intravenous immune globulin (IVIG)
	2nd	rituximab or cyclophosphamide
	adjunct	lifestyle changes and psychological therapies
	3rd	thrombopoietin agonist or splenectomy

Ongoing		(summary)
	adjunct	**lifestyle changes and psychological therapies**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

joint symptoms and serositis

1st **hydroxychloroquine**

Primary options

» hydroxychloroquine sulfate: 200-400 mg/day orally given in 1-2 divided doses, maximum 6.5 mg/kg/day

» Hydroxychloroquine is recommended for all patients with SLE unless contraindicated.[85]

» The beneficial effects of hydroxychloroquine in SLE include the reduction of constitutional symptoms, and reduced musculoskeletal and mucocutaneous manifestations.[104] Guidance recommends that patients who are in long-standing remission may lower their dose, although no studies have formally addressed this strategy.[85]

» Concerns exist regarding the development of retinal toxicity with hydroxychloroquine therapy.[105] [106] Risk factors include duration of treatment, dose, chronic kidney disease and preexisting retinal or macular disease.[106] Retrospective case-control study data suggest that risk of toxic retinopathy is low for doses below 5.0 mg/kg of real body weight for up to 10 years.[105]

» Ophthalmologic screening (by visual field exam and/or spectral domain-optical coherence tomography) is recommended at baseline, after 5 years, and yearly thereafter in the absence of risk factors for retinal toxicity.[85]

» Can be used in combination with nonsteroidal anti-inflammatory drugs and/or corticosteroids if required.[117] [118]

» Treatment with hydroxychloroquine needs to be sustained, but withdrawal during remissions should be considered.

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Ongoing

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapy.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

» SLE is associated with inadequate levels of serum vitamin D compared with the general population.[89] [90] [91] In patients with SLE, vitamin D supplements reduce disease activity; increase serum levels; and improve levels of inflammatory markers, fatigue, and endothelial function.[91] [92] [93]

» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking

Ongoing

cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT, as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **nonsteroidal anti-inflammatory drug**

Treatment recommended for SOME patients in selected patient group

Primary options

» naproxen: 500 mg orally twice daily when required, maximum 1500 mg/day

Secondary options

» celecoxib: 100-200 mg orally twice daily

» Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as a first-line measure in SLE to control joint stiffness as well as musculoskeletal and serosal pain. Naproxen may be the preferred first-line agent owing to the rare occurrence of aseptic meningitis with ibuprofen.[101] [102] [103]

» Blood pressure should be monitored and NSAIDs should be avoided in patients with hypertension or renal disease.

» If long-term NSAID therapy is indicated, *Helicobacter pylori* eradication and the need for gastroprotection are considered.

» Patients who require an anti-inflammatory and who are at high risk of gastrointestinal ulceration should be given a cyclo-oxygenase-2 (COX-2) inhibitor (e.g., celecoxib) if they are at low cardiovascular risk.

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» methylprednisolone sodium succinate: 250-1000 mg intravenously once daily for 3 days

Ongoing

OR

» prednisone: 5-60 mg orally once daily
Doses vary in SLE depending on the type and severity of organ involvement and higher doses may be required.

» Used when nonsteroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine are inadequate.

» Pulses of intravenous methylprednisolone are recommended to provide immediate therapeutic effect in SLE and enable the use of a lower starting dose of oral corticosteroids.[85]

» The recommended dose and route of administration depends on the type and severity of organ involvement, but for chronic maintenance treatment the dose should be minimized to <7.5 mg/day and, when possible, withdrawn.[85]

» The long-term adverse effects of corticosteroid therapy are well documented, and patients should be counseled regarding risk of hypertension and atherosclerotic disease, hyperglycemia, potential skin changes, infection, mood disorders, disorders of bone and muscle (e.g., osteoporosis, osteonecrosis, myopathy), and ophthalmologic effects (e.g., cataracts, increased ocular pressure, exophthalmos). Caution is advised with corticosteroid use in patients with upper gastrointestinal symptoms, especially if also taking NSAIDs.

» The lowest possible dose to control symptoms should be used for the shortest period of time.

» Can be used in combination with NSAIDs and/or hydroxychloroquine if required.[117] [118]

adjunct **immunosuppressant**

Treatment recommended for SOME patients in selected patient group

Primary options

» methotrexate: 7.5 mg orally/intravenously/subcutaneously once weekly on the same day of each week, increase gradually according to response, maximum 20 mg/week

OR

Ongoing

» azathioprine: 2 mg/kg/day orally, adjust dose according to response

OR

» mycophenolate mofetil: consult specialist for guidance on dose

» The addition of immunosuppressive agents (such as methotrexate, azathioprine, or mycophenolate) should be considered for the treatment of patients with organ-threatening disease, patients not responding to hydroxychloroquine (alone or in combination with corticosteroids), and patients unable to reduce the corticosteroid dose below the acceptable dose for chronic use.[85]

» Early initiation of immunosuppressive agents can expedite the tapering/discontinuation of corticosteroids.[85]

» Methotrexate can be a helpful addition in patients taking oral corticosteroids for arthritis/arthralgia.[119] Patients taking methotrexate should have regular hematologic and liver function testing. Methotrexate use may increase the risk of infection. Abnormal hematologic and/or liver function results may necessitate reduction in prescribed dose.[119] Leucovorin or folic acid (depending on local guidelines) is given to counteract the folate-antagonist action of methotrexate.

adjunct **belimumab or rituximab**

Treatment recommended for SOME patients in selected patient group

Primary options

» belimumab: 10 mg/kg intravenously every 2 weeks for the first 3 doses, then every 4 weeks thereafter; 200 mg subcutaneously once weekly
If transitioning from intravenous to subcutaneous therapy, administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose.

Secondary options

» rituximab: consult specialist for guidance on dose

» Belimumab should be considered as an add-on treatment for patients who have an inadequate response to combination treatment

Ongoing

with hydroxychloroquine and corticosteroids with or without immunosuppressive agents (where inadequate response constitutes residual disease activity not allowing tapering of corticosteroids and/or frequent relapses).[85]

» One Cochrane review concluded that there is moderate- to high-quality evidence that belimumab is associated with clinically meaningful benefit for patients with SLE at 52 weeks compared with placebo. Patients receiving the approved dose showed at least a 4-point reduction in SELENA-SLEDAI score.[111]

» Belimumab significantly reduced organ damage progression compared with standard care in long-term study (5-year analysis) of patients with SLE.[112]

» Rituximab can be considered for patients with organ-threatening, refractory disease or with intolerance/contraindications to standard immunosuppressive agents.[85]

» Consider premedication to attenuate infusion- and hypersensitivity-related reactions.

mucocutaneous disease

1st **hydroxychloroquine**

Primary options

» hydroxychloroquine sulfate: 200-400 mg/day orally given in 1-2 divided doses, maximum 6.5 mg/kg/day

» First-line treatment of skin disease in SLE includes antimalarials (e.g., hydroxychloroquine) with or without systemic corticosteroids (starting dose dependent on the severity of skin involvement) and topical agents (e.g., corticosteroids, calcineurin inhibitors).[85]

» Hydroxychloroquine is recommended for all patients with SLE unless contraindicated.[85]

» The beneficial effects of hydroxychloroquine in SLE include the reduction of constitutional symptoms, and reduced musculoskeletal and mucocutaneous manifestations.[104] Guidance recommends that patients who are in long-standing remission may lower their dose, although no studies have formally addressed this strategy.[85]

» Concerns exist regarding the development of retinal toxicity with hydroxychloroquine

Ongoing

therapy.[105] [106] Risk factors include duration of treatment, dose, chronic kidney disease, and preexisting retinal or macular disease.[106] Retrospective case-control study data suggest that risk of toxic retinopathy is low for doses below 5.0 mg/kg of real body weight for up to 10 years.[105]

» Ophthalmologic screening (by visual field exam and/or spectral domain-optical coherence tomography) is recommended at baseline, after 5 years, and yearly thereafter in the absence of risk factors for retinal toxicity.[85]

» Can be used alone or in combination with corticosteroids if required.[117] [118]

» Treatment with hydroxychloroquine needs to be sustained, but withdrawal during remissions should be considered.

plus **topical corticosteroid or calcineurin inhibitor**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydrocortisone topical: (1%) apply to affected area(s) once or twice daily
May be used on eyelids.

OR

» triamcinolone topical: (0.1%) apply to the affected area(s) once or twice daily
May be used on face and neck.

OR

» betamethasone valerate topical: (0.1%) apply to the affected area(s) once or twice daily
May be used on body/limbs and scalp. Can be used on the face if other treatments are ineffective.

OR

» clobetasol topical: (0.05%) apply to the affected area(s) twice daily
May be used on body/limbs or scalp.

OR

MANAGEMENT

Ongoing

» tacrolimus topical: (0.03%, 0.1%) apply to the affected area(s) twice daily

» First-line treatment of skin disease includes the use of topical agents (e.g., corticosteroids, calcineurin inhibitors).[85]

» Topical corticosteroids of different potencies may be used in combination depending on the patient's symptoms. Potent corticosteroids (e.g., betamethasone valerate 0.1%) and very potent corticosteroids (e.g., clobetasol propionate 0.05%) are often used to treat the trunk and limbs including the hands, as well as the scalp. Moderate-potency corticosteroids (e.g., triamcinolone acetonide 0.1%) are used in areas more prone to atrophy such as the face and neck. Mild-potency corticosteroids (e.g., hydrocortisone 1%) are typically reserved for the eyelids, although may prove insufficient. Scalp involvement may be treated with foam or lotion formulations.

plus **lifestyle changes, supportive care, and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» For patients with mucocutaneous manifestations, effective protection from ultraviolet exposure with broad-spectrum sunscreens and smoking cessation are strongly recommended.[85]

» A thorough oral care regime is recommended for all symptomatic patients.[120] Mouthwashes (e.g., chlorhexidine), basic oral hygiene, and regular attendance at a dental practitioner are helpful in the treatment of mouth ulceration.

» Lidocaine ointment may be beneficial for the management of pain secondary to major oral aphthae.[121]

» Artificial saliva preparations may be required for those with dry mouth.[120]

» Hypromellose eye drops are recommended for dry eyes.

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5

Ongoing

servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

» SLE is associated with inadequate levels of serum vitamin D compared with the general population.[89] [90] [91] In patients with SLE, vitamin D supplements reduce disease activity; increase serum levels; and improve levels of inflammatory markers, fatigue, and endothelial function.[91] [92] [93]

» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

MANAGEMENT

Ongoing

» methylprednisolone sodium succinate: 250-1000 mg intravenously once daily for 3 days

OR

» prednisone: 5-60 mg orally once daily
Doses vary in SLE depending on the type and severity of organ involvement and higher doses may be required.

» Can be used when other symptom-relieving measures have failed.

» Pulses of intravenous methylprednisolone are recommended to provide immediate therapeutic effect in SLE and enable the use of a lower starting dose of oral corticosteroids.[85]

» The recommended dose and route of administration depends on the type and severity of organ involvement, but for chronic maintenance treatment the dose should be minimized to <7.5 mg/day and, when possible, withdrawn.[85]

» The long-term adverse effects of corticosteroid therapy are well documented, and patients should be counseled regarding risk of hypertension and atherosclerotic disease, hyperglycemia, potential skin changes, infection, mood disorders, disorders of bone and muscle (e.g. osteoporosis, osteonecrosis, myopathy), and ophthalmologic effects (e.g., cataracts, increased ocular pressure, exophthalmos). Caution is advised with corticosteroid use in patients with upper gastrointestinal symptoms, especially if also taking nonsteroidal anti-inflammatory drugs.

» The lowest possible dose to control symptoms should be used for the shortest period of time. Can be used in combination with hydroxychloroquine if required.[117] [118]

adjunct **immunosuppressant or dapsone or a retinoid**

Treatment recommended for SOME patients in selected patient group

Primary options

» methotrexate: 7.5 mg orally/intravenously/subcutaneously once weekly on the same day of each week, increase gradually according to response, maximum 20 mg/week

Ongoing

OR

» azathioprine: 2 mg/kg/day orally, adjust dose according to response

OR

» mycophenolate mofetil: consult specialist for guidance on dose

Secondary options

» acitretin: consult specialist for guidance on dose

OR

» dapsone: consult specialist for guidance on dose

» For those patients who do not respond to first-line treatment, or require high-dose corticosteroids, methotrexate, azathioprine, mycophenolate, dapsone, or a retinoid (e.g., acitretin) can be added.[85]

» Early initiation of immunosuppressive agents can expedite the tapering/discontinuation of corticosteroids.[85]

» Patients taking methotrexate should have regular hematologic and liver function testing. Methotrexate use may increase the risk of infection. Abnormal hematologic and/or liver function results may necessitate reduction in prescribed dose.[119] Leucovorin or folic acid (depending on local guidelines) is given to counteract the folate-antagonist action of methotrexate.

adjunct **belimumab or rituximab**

Treatment recommended for SOME patients in selected patient group

Primary options

» belimumab: 10 mg/kg intravenously every 2 weeks for the first 3 doses, then every 4 weeks thereafter; 200 mg subcutaneously once weekly
If transitioning from intravenous to subcutaneous therapy, administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose.

Secondary options

MANAGEMENT

Ongoing

» rituximab: consult specialist for guidance on dose

» Guidance suggests that belimumab and rituximab have also shown efficacy in mucocutaneous manifestations of SLE, although rituximab may be less efficacious in chronic forms of skin lupus.[85]

» Consider premedication to attenuate infusion- and hypersensitivity-related reactions.

adjunct **thalidomide**

Treatment recommended for SOME patients in selected patient group

Primary options

» thalidomide: consult specialist for guidance on dose

» Thalidomide should be considered only as a rescue therapy for patients who have failed multiple previous agents due to its strict contraindication in pregnancy, the risk for irreversible polyneuropathy, and the frequent relapses on drug discontinuation.[85]

lupus nephritis

1st **induction therapy**

Primary options

» cyclophosphamide: consult specialist for guidance on dose

OR

» mycophenolate mofetil: consult specialist for guidance on dose

Secondary options

» tacrolimus: consult specialist for guidance on dose

OR

» cyclosporine modified: consult specialist for guidance on dose

OR

» mycophenolate mofetil: consult specialist for guidance on dose
-and-

Ongoing

» tacrolimus: consult specialist for guidance on dose

» For renal manifestations of SLE, induction therapy is required to achieve complete or partial response, followed by immunosuppression to maintain the response. An early significant drop in proteinuria (to ≤1 g/day at 6 months or ≤0.8 g/day at 12 months) is a predictor of favorable long-term renal outcome.[85]

» Mycophenolate or low-dose intravenous cyclophosphamide are recommended as initial induction treatment, as they have the best efficacy/toxicity ratio.[85] [123] [124] [Evidence C] Therapeutic regimens considered for patients at high risk for renal failure are similar, but high-dose intravenous cyclophosphamide can be used.[85]

» One systematic review and meta-analysis found that mycophenolate significantly increased the level of serum complement C3 compared with cyclophosphamide.[125] Mycophenolate was also superior to cyclophosphamide with respect to secondary end points of complete remission and adverse reactions.

» Cyclophosphamide should be given with adequate fluid and mesna (a uroprotective agent) as there is a risk of uro-epithelial toxicity (e.g., hemorrhagic cystitis). Young women should be advised about the risks of amenorrhea or premature ovarian failure with cyclophosphamide; gynecologic referral may be required for further in-depth discussion. Male patients should also be counseled regarding possible risk of infertility. The risk of amenorrhea is lower with mycophenolate, although there are concerns about congenital malformations if it is given during pregnancy.

» Calcineurin inhibitors (e.g., cyclosporine) may be considered as second-line agents for induction therapy in membranous lupus nephritis, podocytopathy, or proliferative disease with refractory nephrotic syndrome despite standard-of-care within 3 to 6 months.[85] Calcineurin inhibitors may be used alone, or in combination with mycophenolate, to treat proliferative lupus nephritis.[129] [130] [131] [132] [133] [134]

» For patients with refractory nephrotic syndrome, tacrolimus may be used alone or in combination with mycophenolate, as this combination is effective in disease refractory to standard therapy.[85] [135]

Ongoing

» Monitoring serum creatinine and blood levels of patients being treated with calcineurin inhibitors is essential to avoid chronic drug toxicity.[85]

plus **hydroxychloroquine**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydroxychloroquine sulfate: 200-400 mg/day orally given in 1-2 divided doses, maximum 6.5 mg/kg/day

» Continued hydroxychloroquine is associated with increased remission rates in patients initially treated with mycophenolate for lupus nephritis.[127]

plus **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» methylprednisolone sodium succinate: 250-1000 mg intravenously once daily for 3 days

OR

» prednisone: 5-60 mg orally once daily Doses vary in SLE depending on the type and severity of organ involvement and higher doses may be required.

» Corticosteroids are also given as part of the induction regimen in addition to background treatment with hydroxychloroquine.[82] [126]

» Initial therapy with pulse doses of intravenous methylprednisolone is encouraged.[85]

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

Ongoing

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

» SLE is associated with inadequate levels of serum vitamin D compared with the general population.[89] [90] [91] In patients with SLE, vitamin D supplements reduce disease activity; increase serum levels; and improve levels of inflammatory markers, fatigue, and endothelial function.[91] [92] [93]

» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression,

Ongoing

pain, and quality of life for patients with SLE.[97] [98]

plus **maintenance therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» azathioprine: consult specialist for guidance on dose

OR

» mycophenolate mofetil: consult specialist for guidance on dose

Secondary options

» tacrolimus: consult specialist for guidance on dose

OR

» cyclosporine modified: consult specialist for guidance on dose

» Once a patient has attained complete or partial response, immunosuppression is continued to maintain the response.

» Mycophenolate or azathioprine are recommended first-line for maintenance therapy, and should be used in combination with corticosteroids.[85] Either treatment can be used for maintenance therapy after induction with cyclophosphamide or mycophenolate and is more effective in preserving renal function than corticosteroids alone.[136]

» Calcineurin inhibitors (e.g., tacrolimus, cyclosporine) may be considered as second-line agent for maintenance therapy in membranous lupus nephritis, podocytopathy, or proliferative disease with refractory nephrotic syndrome despite standard-of-care within 3 to 6 months.[85]

» One systematic review and meta-analysis of the effect of calcineurin inhibitors for the induction and maintenance treatment of lupus nephritis found that calcineurin inhibitor treatment during the maintenance period was as effective as azathioprine treatment, with a much lower risk of adverse effects.[131]

» Monitoring serum creatinine and blood levels of patients being treated with calcineurin

Ongoing

inhibitors to avoid chronic drug toxicity is essential.[85]

adjunct **belimumab or rituximab**

Treatment recommended for SOME patients in selected patient group

Primary options

» belimumab: 10 mg/kg intravenously every 2 weeks for the first 3 doses, then every 4 weeks thereafter; 400 mg subcutaneously once weekly for the first 4 doses, then 200 mg once weekly thereafter
If transitioning from intravenous to subcutaneous therapy, administer the first subcutaneous dose (200 mg) 1 to 2 weeks after the last intravenous dose. A patient may transition from intravenous to subcutaneous therapy any time after receipt of the first 2 intravenous doses.

Secondary options

» rituximab: consult specialist for guidance on dose

» Belimumab is approved for adults with lupus nephritis. It should be considered as an add-on treatment for patients who have an inadequate response to combination treatment with hydroxychloroquine and corticosteroids with or without immunosuppressive agents, defined as residual disease activity not allowing tapering of corticosteroids and/or frequent relapses.[85]

» In a randomized double-blind trial, significantly more patients who received belimumab plus standard therapy had a renal response (43% vs. 32%; defined as ratio of urinary protein to creatinine of 0.7 or less, an estimated glomerular filtration rate that was no worse than 20% below the pre-flare value or at least 60 mL/minute/1.73 m², and no use of rescue therapy for treatment failure) compared with standard therapy alone.[128]

» Rituximab can be considered for patients with organ-threatening, refractory disease or with intolerance/contraindications to standard immunosuppressive agents.[85]

» Consider premedication to attenuate infusion- and hypersensitivity-related reactions.

neuropsychiatric lupus

MANAGEMENT

Ongoing

inflammatory only **1st** **immunosuppressant**

Primary options

» methotrexate: 7.5 mg orally/intravenously/subcutaneously once weekly on the same day of each week, increase gradually according to response, maximum 20 mg/week

OR

» azathioprine: 2 mg/kg/day orally, adjust dose according to response

OR

» mycophenolate mofetil: consult specialist for guidance on dose

Secondary options

» cyclophosphamide: consult specialist for guidance on dose

» Treatment of SLE-related neuropsychiatric disease includes immunosuppressive agents and corticosteroids for manifestations considered to reflect an inflammatory process.[85] The choice of immunosuppressive agent (e.g., azathioprine, mycophenolate, methotrexate) will depend on individual cases, as the neuropsychiatric manifestations can be varied.

» Distinction between the two pathophysiologic processes (inflammatory and atherothrombotic/antiphospholipid-related manifestations) may be difficult in practice. The two processes could coexist in the same patient.

» Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as rescue therapy in patients not responding to other immunosuppressive agents.[85]

plus **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» methylprednisolone sodium succinate: 250-1000 mg intravenously once daily for 3 days

OR

Ongoing

» prednisone: 5-60 mg orally once daily
Doses vary in SLE depending on the type and severity of organ involvement and higher doses may be required.

» Treatment of SLE-related neuropsychiatric disease includes corticosteroids for manifestations considered to reflect an inflammatory process.[85]

» Initial therapy with pulse doses of intravenous methylprednisolone is encouraged.[85]

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

» SLE is associated with inadequate levels of serum vitamin D compared with the general population.[89] [90] [91] In patients with SLE, vitamin D supplements reduce disease activity; increase serum levels; and improve levels of inflammatory markers, fatigue, and endothelial function.[91] [92] [93]

» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

Ongoing

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **rituximab**

Treatment recommended for SOME patients in selected patient group

Primary options

» rituximab: consult specialist for guidance on dose

» Rituximab can be considered for patients with organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents. Evidence of benefit in severe refractory neuropsychiatric SLE is limited to case reports.

adjunct **intravenous immune globulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): consult specialist for guidance on dose

Ongoing

» IVIG may be used as adjunctive therapy when initial treatment is inadequate, but the quality of evidence supporting its use is poor (small cohort studies).[137] IVIG can be effective in the treatment of SLE-associated peripheral neuropathies.

adjunct **plasmapheresis**

Treatment recommended for SOME patients in selected patient group

» Plasmapheresis may also be considered as an adjunctive treatment.[137] The aim of the treatment is to remove circulating autoantibodies. Recommended if there are clinical and investigative findings consistent with cerebral vasculitis, and may be used when earlier treatments are inadequate. Data from large randomized trials are lacking.

adjunct **targeted symptomatic pharmacotherapy**

Treatment recommended for SOME patients in selected patient group

» Targeted symptomatic therapy is indicated according to the type of manifestation.[85]

» Antidepressants, anticonvulsants, antipsychotics, or antimigraine therapies should be prescribed on the advice of relevant specialists on an individual patient basis.

atherothrombotic/ antiphospholipid-related manifestations only

1st **antiplatelet agent or anticoagulation**

» Treatment of SLE-related neuropsychiatric disease includes an antiplatelet agent/ anticoagulant for atherothrombotic/ antiphospholipid-related manifestations.

» Distinction between the two pathophysiologic processes (inflammatory and atherothrombotic/ antiphospholipid-related manifestations) may be difficult in practice. The two processes could coexist in the same patient.

» Consult a hematologist for guidance on specific antiplatelet agent/anticoagulant treatment regimens.

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

Ongoing

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

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» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase

Ongoing

suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **immunosuppressant**

Treatment recommended for SOME patients in selected patient group

» Patients with SLE with cerebrovascular disease should be managed like the general population in the acute phase; in addition to controlling extra-central nervous system lupus activity, immunosuppressive therapy may be considered in the absence of antiphospholipid antibodies and other atherosclerotic risk factors or in recurrent cerebrovascular events.[85] Consult a specialist for guidance on choice of regimen.

adjunct **intravenous immune globulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): consult specialist for guidance on dose

» IVIG administration has also been used in patients with SLE. The quality of evidence for use of IVIG is poor (entirely from small cohort studies). However, it may be used as an adjunctive therapy when initial treatment is inadequate.[137] IVIG can be effective in the treatment of SLE-associated peripheral neuropathies.

adjunct **plasmapheresis**

Treatment recommended for SOME patients in selected patient group

» Plasmapheresis may also be considered as an adjunctive treatment.[137] The aim of the treatment is to remove circulating autoantibodies. Recommended if there are clinical and investigatory findings consistent with cerebral vasculitis, and may be used when earlier treatments are inadequate. Data from large randomized trials are lacking.

adjunct **targeted symptomatic pharmacotherapy**

Treatment recommended for SOME patients in selected patient group

Ongoing

» Targeted symptomatic therapy is indicated according to the type of manifestation.[85]

» Antidepressants, anticonvulsants, antipsychotics, or antimigraine therapies should be prescribed on the advice of relevant specialist on an individual patient basis.

inflammatory and atherothrombotic/ antiphospholipid-related manifestations

1st **immunosuppressant**

» The combination of an immunosuppressive agent and antiplatelet/anticoagulant therapy may be considered in these patients.[85] Consult a specialist for guidance on choice of immunosuppressant regimen.

» Distinction between the two pathophysiologic processes (inflammatory and atherothrombotic/ antiphospholipid-related manifestations) may be difficult in practice. The two processes could coexist in the same patient.

plus **antiplatelet agent or anticoagulation**

Treatment recommended for ALL patients in selected patient group

» Treatment of SLE-related neuropsychiatric disease includes an antiplatelet agent/ anticoagulant for atherothrombotic/ antiphospholipid-related manifestations. Consult a hematologist for guidance on specific antiplatelet/anticoagulant treatment regimens.

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of

Ongoing

oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

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» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

» Patients who smoke should be encouraged to stop. Evidence suggests smoking is associated with more active disease, and a significant reduction in the therapeutic effect of hydroxychloroquine.[44] [99] [100] Smoking cessation reduces the risk of atherosclerotic vascular disease.

» SLE has a significant impact on health-related quality of life, and has been shown to increase suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **rituximab**

Treatment recommended for SOME patients in selected patient group

Primary options

» rituximab: consult specialist for guidance on dose

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» Rituximab can be considered for patients with organ-threatening, refractory disease or with intolerance/contraindications to standard immunosuppressive agents. Evidence of benefit in severe refractory neuropsychiatric SLE is limited to case reports.

adjunct **intravenous immune globulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): consult specialist for guidance on dose

» IVIG may be used as adjunctive therapy when initial treatment is inadequate, but the quality of evidence supporting its use is poor (small cohort studies).[137] IVIG can be effective in the treatment of SLE-associated peripheral neuropathies.

adjunct **plasmapheresis**

Treatment recommended for SOME patients in selected patient group

» Plasmapheresis may also be considered as an adjunctive treatment.[137] The aim of the treatment is to remove circulating autoantibodies.

» Recommended if there are clinical and investigative findings consistent with cerebral vasculitis, and may be used when earlier treatments are inadequate. Data from large randomized trials are lacking.

adjunct **targeted symptomatic pharmacotherapy**

Treatment recommended for SOME patients in selected patient group

» Targeted symptomatic therapy is indicated according to the type of manifestation.[85]

» Antidepressants, anticonvulsants, antipsychotics, or antimigraine therapies should be prescribed on the advice of relevant specialist on an individual patient basis.

hematologic manifestations

1st **immunosuppressant**

Primary options

» azathioprine: 2 mg/kg/day orally, adjust dose according to response

OR

Ongoing

» mycophenolate mofetil: consult specialist for guidance on dose

OR

» cyclosporine modified: consult specialist for guidance on dose

» Hematologic manifestations that require anti-inflammatory/immunosuppressive treatment in patients with SLE include thrombocytopenia and autoimmune hemolytic anemia.[85]

» Treatment of significant lupus thrombocytopenia (platelet count below 30,000/mm³) and autoimmune hemolytic anemia consists of an immunosuppressive agent (e.g., azathioprine, mycophenolate, cyclosporine) as a corticosteroid-sparing agent, in combination with a corticosteroid.[85]

plus **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» methylprednisolone sodium succinate: 250-1000 mg intravenously once daily for 3 days

OR

» prednisone: 5-60 mg orally once daily
Doses vary in SLE depending on the type and severity of organ involvement and higher doses may be required.

» Treatment of significant lupus thrombocytopenia (platelet count below 30,000/mm³) and autoimmune hemolytic anemia consists of moderate/high doses of corticosteroids. Initial therapy with pulse doses of intravenous methylprednisolone is encouraged.[85]

plus **lifestyle changes and psychological therapies**

Treatment recommended for ALL patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

Ongoing

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

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» SLE has a significant impact on health-related quality of life, and has been shown to increase

Ongoing

suicidal ideation and suicide attempts.[95] [96] Literature reviews suggest that psychological interventions such as psychotherapy, cognitive behavioral therapies (CBT), psychoeducation, and mindfulness-based CBT), as adjuncts to medical therapy, improve fatigue, depression, pain, and quality of life for patients with SLE.[97] [98]

adjunct **intravenous immune globulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): consult specialist for guidance on dose

» IVIG may be considered in the acute phase, in cases of inadequate response to high-dose corticosteroids or to avoid corticosteroid-related infectious complications.[85]

2nd **rituximab or cyclophosphamide**

Primary options

» rituximab: consult specialist for guidance on dose

OR

» cyclophosphamide: consult specialist for guidance on dose

» Cyclophosphamide should be considered in patients with no response to corticosteroids or patients who have relapsed.[85]

» Rituximab can be considered for patients with organ-threatening, refractory disease or with intolerance/contraindications to standard immunosuppressive agents.[85]

adjunct **lifestyle changes and psychological therapies**

Treatment recommended for SOME patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

Ongoing

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

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Ongoing

pain, and quality of life for patients with SLE.[97] [98]

3rd **thrombopoietin agonist or splenectomy**

Primary options

» eltrombopag: consult specialist for guidance on dose

OR

» romiplostim: consult specialist for guidance on dose

» Thrombopoietin agonists (e.g., eltrombopag, romiplostim) or splenectomy should be reserved as last options.[85]

adjunct **lifestyle changes and psychological therapies**

Treatment recommended for SOME patients in selected patient group

» Lifestyle changes include dietary advice, smoking cessation, sun protection, exercise, and psychological therapies.

» Exposure to ultraviolet light may exacerbate or induce systemic manifestations of SLE.[86] Patients with SLE should be advised to avoid excessive sun exposure and to use a broad-spectrum sunscreen.[87]

» No dietary measures have been shown to alter the course of SLE. However, the late complications of premature cardiovascular disease should be borne in mind. Patients should be advised to maintain an ideal body weight for their height and reduce salt intake if hypertension due to renal disease is present. General advice includes eating at least 5 servings of fruit or vegetables per day, replacing saturated fats with monounsaturates and polyunsaturates, and increasing the amount of oily fish eaten; a diet rich in polyunsaturated fatty acids should be recommended.[88] Standard advice for the amount of alcohol per week for men and women should be given.

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Ongoing

» Some evidence suggests that omega-3 fatty acid supplementation may reduce SLE disease activity.[92] [94]

» Herbal preparations should be avoided. They can interact adversely with pharmacologic agents and may cause harm.

» Patients with stable SLE should be advised to avoid a sedentary lifestyle and to undertake supervised exercise.[88] In these patients, adherence to exercise guidelines should be encouraged to maintain optimum cardiovascular fitness. This should include ≥30 minutes of moderate physical activity ≥5 times per week; patients are advised to stop exercising if they experience pain or discomfort.

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Emerging

Anifrolumab

Anifrolumab, a monoclonal antibody type I interferon receptor antagonist, is approved by the US Food and Drug Administration (FDA) for the treatment of adults with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy. The European Medicines Agency has approved anifrolumab as an add-on therapy for adults with moderate to severe, active autoantibody-positive SLE despite standard treatment. In randomized placebo-controlled phase 3 trials, anifrolumab reduced oral corticosteroid dose and severity of skin disease, and improved disease response at 52 weeks, in patients with moderate to severe SLE.[139] [140] Long-term anifrolumab treatment suggests an acceptable safety profile with sustained improvement in SLE disease activity, health-related quality of life, and serologic measures.[141]

Voclosporin

Voclosporin, a novel oral calcineurin inhibitor, is approved by the FDA for the treatment of adults with active lupus nephritis in combination with an immunosuppressive therapy regimen. In a phase 3 randomized controlled trial (RCT) of patients with lupus nephritis, voclosporin in combination with mycophenolate and low-dose corticosteroid led to a clinically significant superior complete renal response at week 52 compared with mycophenolate and low-dose corticosteroid alone (73 [41%] of 179 patients vs. 40 [23%] of 178 patients, respectively).[142]

Baricitinib

Baricitinib is an oral selective inhibitor of Janus kinase (JAK) that blocks JAK-1 and JAK-2. It is licensed for use in many countries for the treatment of adults with rheumatoid arthritis.[143] [144] [145] [146] One 24-week placebo-controlled phase 2 RCT of baricitinib reported significant improvements in signs and symptoms of SLE among patients assigned to a high dose of baricitinib.[147] Phase 3 trials are ongoing.[148] [149] Baricitinib has been granted fast-track designation by the FDA for the treatment of SLE.

Obinutuzumab

Obinutuzumab is a monoclonal antibody that targets CD20, a protein found on specific B cells. It has been granted breakthrough-therapy designation for adults with lupus nephritis by the FDA. Data from the phase 2 NOBILITY study in adult patients with proliferative lupus nephritis (n=127) indicate that obinutuzumab, in combination with standard of care (mycophenolate and a corticosteroid), is associated with enhanced complete renal response rates at 12 months compared with standard care alone.[150] Results at 2 years suggest that the benefit is maintained.[151]

Itolizumab

Itolizumab is a humanized immunoglobulin G1 monoclonal antibody. It selectively targets CD6, the novel immune checkpoint receptor that plays a central role in modulating the activity and trafficking of T cells that drive several immuno-inflammatory diseases. Itolizumab has been granted fast-track designation by the FDA for the treatment of lupus nephritis. A phase 1b dose escalation study to evaluate the safety and tolerability of itolizumab in patients with SLE with or without proliferative nephritis is ongoing.[152]

Blisibimod

Blisibimod is a potent and selective inhibitor of B-cell activating factor (BAFF). BAFF is a mediator of differentiation, maturation, and survival of B cells. Blisibimod did not meet the primary end point (improvement in the SLE responder index at week 52) in a phase 3 RCT of 442 patients with high SLE disease activity (n=442).[153]

Primary prevention

SLE is a multisystem autoimmune disease with unclear etiology and complex immune dysregulation and, as yet, there are no preventive strategies.

European League Against Rheumatism guidelines suggest low-dose aspirin may be considered for prevention of thrombosis and miscarriage in patients with SLE and antiphospholipid antibodies.[47]

Secondary prevention

Immunizations have implications for people who have SLE.

- Tetanus toxoid, pneumococcal, and *Haemophilus influenzae* B vaccines have been demonstrated to be safe and effective when given to patients with SLE.[180]
- The influenza vaccine and pneumococcal vaccine have been shown to be safe but have reduced efficacy.[181] [182] The immunogenicity of influenza vaccine in patients with SLE appears to vary with viral strain.[183] [184]
- Several case reports document concerns that hepatitis B vaccination may lead to an exacerbation of SLE, so it is not recommended.[185]
- Live vaccines (shingles, yellow fever, intranasal influenza) are not to be used because of underlying or imposed immunosuppression.

Patient discussions

As with any other chronic disease, establishing a partnership with the patient to improve their health is an important part of the management plan. Patient education is fundamental and directing patients to useful resources should be encouraged. The Lupus Foundation website is a useful resource. [Lupus Foundation of America] (https://www.lupus.org)

- Patients with SLE should be advised to avoid excessive sun exposure and to use a sunblock with a sun protection factor (SPF) of ≥15. They should also be aware that certain drugs can exacerbate the disorder.
- In women of reproductive age, conception, and pregnancy-related issues should be discussed early in the disease course so that specialist advice can be given and patients counseled regarding outcomes in relation to disease-related activity. Studies suggest that patients with SLE with stable disease can safely use oral contraceptives.[177] [178] Patients with active disease and patients at risk for thrombosis should avoid the use of oral contraceptives.
- Although >50% of all lupus pregnancies are completely normal, all pregnant lupus patients would be considered high risk and be managed by a specialist obstetric team. Pregnant lupus patients should continue on hydroxychloroquine throughout pregnancy.[179]
- Patients who smoke should be encouraged to adopt strategies to stop, as SLE is associated with higher than expected late cardiovascular risk as well as worsening Raynaud symptoms and lupus-related skin disease.
- Symptoms of concern should be outlined and are discussed in the Lupus Foundation website. [Lupus Foundation of America] (https://www.lupus.org)

FOLLOW UP

Monitoring

Monitoring

Structured methods for following patients with SLE have been developed that take into account previous damage as well as ongoing disease activity. Several are available:

- Systemic Lupus International Collaborating Clinics (SLICC, endorsed by the American College of Rheumatology), which can be downloaded from the college's website [American College of Rheumatology] (http://www.rheumatology.org)
- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)
- British Isles Lupus Assessment Group (BILAG) index
- Systemic Lupus Activity Measure (SLAM).

There is as yet no consensus on the value of serologic tests and complement levels to follow up patients. In general terms, changing levels should prompt more vigilant monitoring.

In assessing a patient with a presumed flare of symptoms, it is important to exclude infection and comorbidity as an explanation.

Patients with lupus nephritis should have their renal function monitored (renal biopsy, kidney function tests, urinalysis).

Complications

Complications	Timeframe	Likelihood
anemia	**long term**	**high**
Typically secondary to chronic disease and improves with control of disease activity.		
leukopenia	**long term**	**high**
Typically due to lymphopenia, and to a lesser extent neutropenia.		
thrombocytopenia	**long term**	**high**
Frequently seen in SLE, but other causes should be excluded.		
corticosteroid-related cataracts	**long term**	**medium**
Long-term corticosteroid therapy is a recognized cause of posterior subcapsular cataract. However, there is no evidence to suggest that patients with SLE are at higher risk.		
corticosteroid-related osteoporosis	**long term**	**medium**
Guidelines for prevention and treatment of corticosteroid-induced osteoporosis should be followed.		
corticosteroid-related diabetes mellitus	**long term**	**medium**
High-dose corticosteroid therapy can result in insulin resistance and type 2 diabetes mellitus.		
amenorrhea secondary to cyclophosphamide	**long term**	**medium**
Increased risk of premature ovarian failure and sustained hypergonadotrophic amenorrhea with increased cumulative dose and increased age of patient: <50% of patients age <30 years, 60% patients age 30 to 40 years.[169] [170]		
male infertility secondary to cyclophosphamide and/or disease	**long term**	**medium**
This is well documented. A male patient requiring cyclophosphamide should be counseled prior to starting therapy and discussions raised regarding sperm storage prior to treatment commencing. SLE itself is associated with an increased frequency of sperm abnormality and reduced testicular volume. Post-pubertal cyclophosphamide is a major contributor to reduced fertility in male patients with SLE.[171]		
pericarditis	**long term**	**medium**
May occur as part of serositis. Treated as per patients with serositis, with additional cardiovascular specialist input.		

FOLLOW UP

Complications	Timeframe	Likelihood
myocarditis	**long term**	**medium**
May occur as part of cardiopulmonary manifestations. Requires cardiovascular specialist input. Other causes need to be excluded.		
endocarditis	**long term**	**medium**
May occur as part of cardiopulmonary manifestations. Requires cardiovascular specialist input. Other causes need to be excluded.		
pleuritis	**long term**	**medium**
Can be either unilateral or bilateral. It is more common than pericarditis.		
pleural effusion	**long term**	**medium**
Pleural effusions in SLE are usually unilateral and generally exudative. Other causes of a pleural effusion should be excluded.		
malignancy secondary to cyclophosphamide or azathioprine	**long term**	**low**
Immunosuppressives such as azathioprine and cyclophosphamide can increase the risk of malignancy in patients with SLE.[164] Patients should be counseled on the risk before commencing this therapy and specialist oncology input sought if concerns for malignancy exist after therapy.		
corticosteroid-related avascular necrosis	**long term**	**low**
Corticosteroid therapy is associated with an increased risk of avascular necrosis of bone, most commonly in the femoral head but described at other sites. An association with antiphospholipid antibody syndrome is also recognized.		
hemolytic anemia	**long term**	**low**
Although not a common complication, can be very severe.		
progressive multifocal leukoencephalopathy (PML)	**long term**	**low**
A rare viral brain disease that is a potential adverse effect of some disease modifying drugs, particularly rituximab. A literature review suggests an increased risk of PML in patients with SLE compared with the general population, potentially due to immunosuppression, underlying disease, treatments to manage disease, or some combination of these factors.[176]		

Complications	Timeframe	Likelihood
Raynaud phenomenon	**variable**	**high**
Standard treatment consists of trigger avoidance and lifestyle changes. Alternatives for refractory disease include oral or topical vasodilators (e.g., calcium-channel blockers, topical nitroglycerin). Severe disease may require intravascular prostacyclin or sympathectomy. The phosphodiesterase-5 inhibitor sildenafil may be used for digital necrosis in scleroderma overlap syndrome.		
infection due to immunosuppression	**variable**	**medium**
Corticosteroids, methotrexate, cyclophosphamide, and azathioprine can all increase the risk of infection via myelosuppression. Includes common bacterial infections as well as opportunistic infections: fungi, parasites, mycobacteria, and protozoa. Infection should be treated with therapy as per local guidelines and the immunosuppressant withheld at that time.		
nonsteroidal anti-inflammatory drug (NSAID)-related renal failure	**variable**	**medium**
Treatment with either nonselective-NSAIDs or cyclo-oxygenase-2 (COX-2)-inhibitors increases the risk of renal failure.[165] This therapy should not be commenced in patients with preexisting renal impairment. If renal failure develops, the therapy should be discontinued and appropriate additional treatment for the renal impairment undertaken.		
NSAID-related gastritis	**variable**	**medium**
Patients who require an anti-inflammatory and who are at high risk of gastrointestinal ulceration should be given a cyclo-oxygenase-2 (COX-2) inhibitor (e.g., celecoxib) if they are at low cardiovascular risk.		
fetal loss	**variable**	**medium**
SLE in the presence of antiphospholipid antibodies is associated with up to 42% fetal loss.[172] [173]		
depression	**variable**	**medium**
Depression is more commonly reported in patients with SLE than in healthy controls.[174] Treatment approaches should be similar to those offered to individuals with depression. For depression with psychomotor symptoms, referral for specialist advice should be sought.		
pulmonary hypertension	**variable**	**medium**
Results in heart failure and eventually death. There may be underlying parenchymal involvement due to interstitial lung disease.		

FOLLOW UP

Complications	Timeframe	Likelihood
diffuse interstitial lung disease	**variable**	**medium**
Lupus pneumonitis may present with shortness of breath, cough, and fever.		
fracture risk	**variable**	**medium**
Meta-analysis indicates that SLE is significantly associated with increased fracture risk.[175] Patients with SLE had significantly lower bone mineral density levels than controls in the whole body, the femoral neck, the lumbar spine, and the total hip.[175]		
septic arthritis due to immunosuppression	**variable**	**low**
Atypical infections such as *Salmonella* can occur. Consideration should be given to this complication in a patient with a single swollen joint; systemic symptoms may be masked by corticosteroid therapy. Synovial fluid culture may be negative, especially if prior antibiotics have been prescribed.		
hematuria secondary to cyclophosphamide	**variable**	**low**
Patients on cyclophosphamide are at risk of developing uroepithelial toxicity as well as bladder tumors. The risk can be reduced by concomitant administration of mesna (uroprotective agent) and a fluid load.		
chronic active hepatitis	**variable**	**low**
Has been associated with SLE.		
lupus peritonitis	**variable**	**low**
Abdominal pain, vomiting, and diarrhea may be caused by lupus peritonitis, but other causes of an acute abdomen should be excluded. Although rare, lupus peritonitis may mimic appendicitis.		
pancreatitis secondary to disease or azathioprine	**variable**	**low**
SLE-associated pancreatitis is rare, with an estimated annual incidence of <1 per 1000 lupus patients.[166] The mortality is thought to be higher in lupus than nonlupus patients. Standard assessment of the patient and treatment should be followed. Azathioprine is a recognized cause of pancreatitis. In the majority of cases in patients with SLE, pancreatitis does not seem to be related to steroid or azathioprine therapy, but rather to the disease itself.[167]		
arterial thrombosis	**variable**	**low**
Patients with SLE and antiphospholipid antibody syndrome are at higher risk of arterial thrombosis. Guidelines for treatment should be followed.[168] There is accumulating evidence that patients with established disease are more likely to develop accelerated atherosclerotic vascular disease; it is unclear whether this is disease related or secondary to corticosteroid therapy.		

Complications	Timeframe	Likelihood
venous thrombosis	**variable**	**low**
In a patient with venous thrombosis, tests for antiphospholipid antibody syndrome should be sought and treatment guidelines should be followed.[168]		
tendon rupture	**variable**	**low**
This is a rare but potentially disabling complication. Possible predisposing factors include trauma, corticosteroid therapy, and local inflammation.		
valvular heart disease	**variable**	**low**
Patients with antiphospholipid syndrome are more likely to have valvular heart disease.		
transverse myelitis	**variable**	**low**
Requires emergency treatment, usually intravenous cyclophosphamide plus corticosteroids. Warfarin is used in the presence of antiphospholipid antibodies and plasmapheresis may be used in this setting as well.		
pulmonary hemorrhage	**variable**	**low**
Typically, presents with hemoptysis and anemia. Chest x-ray demonstrates diffuse or focal patchy alveolar infiltrates. Requires specialist management.		

Prognosis

Mortality

A European inception cohort of 1000 patients drawn from 7 countries reported 5-year survival of 95% and 10-year survival of 92%.[158] [159]

Patients with SLE have higher rates of death from all causes, regardless of sex, ethnicity, renal disease, cardiovascular disease, or infection. However, the risk of death due to malignancy is not increased.[160]

The most common cause of mortality is cardiovascular disease, followed closely by infection and severe disease activity.[161] There are differences in survival based on ethnicity, socioeconomic status, age, and sex.

Early mortality is related to active disease (primarily renal and central nervous system), thrombosis, and infection. Later deaths are due to infection and premature atherosclerotic vascular disease; it is yet to be clarified whether this is iatrogenic or due to the underlying disease process.

Mucocutaneous disease

Outcome is determined by the number and severity of systemic complications. 20% of patients with chronic discoid lupus develop systemic disease, usually of the non organ-threatening variety.

Smoking is known to exacerbate skin disease.

Musculoskeletal disease

Tenosynovitis may result in tendon ruptures or, less frequently, Jaccoud arthritis. Correctable ulnar deviation and joint subluxations in the hands in the absence of radiologic damage is characteristic.

Serositis

Persistent exudative pleural and pericardial effusions can arise. Outcome is a function of the local effects of their occurrence.

Renal disease

Outcome is determined by the renal histologic International Society of Nephrology/Renal Pathology Society grade and severity index as well as the extent of renal impairment. Combined treatment with corticosteroids and cyclophosphamide to induce remission and substitution with azathioprine has improved outcome, but other therapeutic strategies to minimize iatrogenic complications are being developed. Improvements in renal replacement therapy have resulted in commensurate improvements in those who progress to endstage renal disease.

Central nervous system (CNS) disease

The presence of CNS manifestations is associated with poorer outcomes, but the site and extent of damage has to be taken into consideration.

Respiratory disease

Patients with SLE-associated pulmonary hypertension have poor long-term survival. Early diagnosis and management are recommended for better outcomes.[162]

Cardiovascular disease

Causes of cardiovascular events in SLE are multifactorial, including both traditional and disease-specific risk factors (presence of autoantibodies and neurologic disorders).[163]

Diagnostic guidelines

International

Canadian Rheumatology Association recommendations for the assessment and monitoring of systemic lupus erythematosus (https://rheum.ca/resources/publications) [81]

Published by: Canadian Rheumatology Association **Last published:** 2018

American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437757) [82]

Published by: American College of Rheumatology **Last published:** 2012

Treatment guidelines

International

Guideline for vaccinations in patients with rheumatic and musculoskeletal diseases (https://rheumatology.org/clinical-practice-guidelines) [154]

Published by: American College of Rheumatology **Last published:** 2023

American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437757) [82]

Published by: American College of Rheumatology **Last published:** 2012

First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus (https://ard.bmj.com/content/77/11/1549) [155]

Published by: Latin American Group for the Study of Lupus; Pan-American League of Associations of Rheumatology **Last published:** 2018

Clinical practice guidelines for the treatment of systemic lupus erythematosus (https://www.ncbi.nlm.nih.gov/pubmed/29735288) [156]

Published by: Mexican College of Rheumatology **Last published:** 2018

2019 update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis (https://www.eular.org/recommendations_management.cfm) [126]

Published by: European League Against Rheumatism; European Renal Association – European Dialysis and Transplant Association **Last published:** 2020

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus (https://www.eular.org/recommendations_management.cfm) [85]

Published by: European League Against Rheumatism **Last published:** 2019

EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome (https://www.eular.org/recommendations_management.cfm) [157]

Published by: European League Against Rheumatism **Last published:** 2017

Online resources

1. Lupus Foundation of America (https://www.lupus.org) *(external link)*
2. NIH: systemic lupus erythematosus (lupus) (https://www.niams.nih.gov/health-topics/lupus) *(external link)*
3. CDC: systemic lupus erythematosus (SLE) (https://www.cdc.gov/lupus/facts/detailed.html) *(external link)*
4. American College of Rheumatology (http://www.rheumatology.org) *(external link)*

EVIDENCE TABLES

Evidence tables

How do mycophenolate and cyclophosphamide compare as induction therapies for people with lupus nephritis?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.2237/full)

Evidence C *

Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Adolescents and adults with lupus nephritis
Intervention: Oral mycophenolate [a]
Comparison: Intravenous cyclophosphamide [a]

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
All-cause mortality (mean follow-up 24 weeks)	No statistically significant difference	Very Low
End-stage kidney disease (mean follow-up 32 weeks)	No statistically significant difference	Very Low
Renal relapse	No statistically significant difference	GRADE assessment not performed for this outcome
Stable kidney function	No statistically significant difference	GRADE assessment not performed for this outcome
Renal remission: complete or partial (mean follow-up 24 weeks)	No statistically significant difference	Low
Renal remission: complete or partial remission in proteinuria (mean follow-up 24 weeks)	No statistically significant difference	GRADE assessment not performed for this outcome
Daily proteinuria	No statistically significant difference	GRADE assessment not performed for this outcome

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Adverse effects/toxicity: ovarian failure (mean follow-up 24 weeks)	No statistically significant difference	Very Low
Adverse effects/toxicity: alopecia (mean follow-up 24 weeks)	Occurs more commonly with cyclophosphamide compared with mycophenolate (favors intervention)	Moderate
Adverse effects/toxicity: leukopenia (mean follow-up 24 weeks)	No statistically significant difference	GRADE assessment not performed for this outcome
Adverse effects/toxicity: diarrhea (mean follow-up 24 weeks)	Occurs more commonly with mycophenolate compared with cyclophosphamide (favors comparison)	Moderate
Doubling of serum creatinine, Adverse effects/toxicity (bone toxicity)	-	None of the studies identified by the review assessed these outcomes

Note
The Cochrane Clinical Answer (CCA) also compared oral mycophenolate with oral cyclophosphamide as first-line induction for proliferative lupus nephritis. They found one small RCT (62 people) that had similar results with no statistically significant difference between groups for all-cause mortality or renal outcomes.

[a] This evidence table summarizes the findings for the comparison of oral mycophenolate versus intravenous cyclophosphamide, which is the main comparison as stated in the Cochrane review Summary of Findings table. See the full CCA for more information.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

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Images

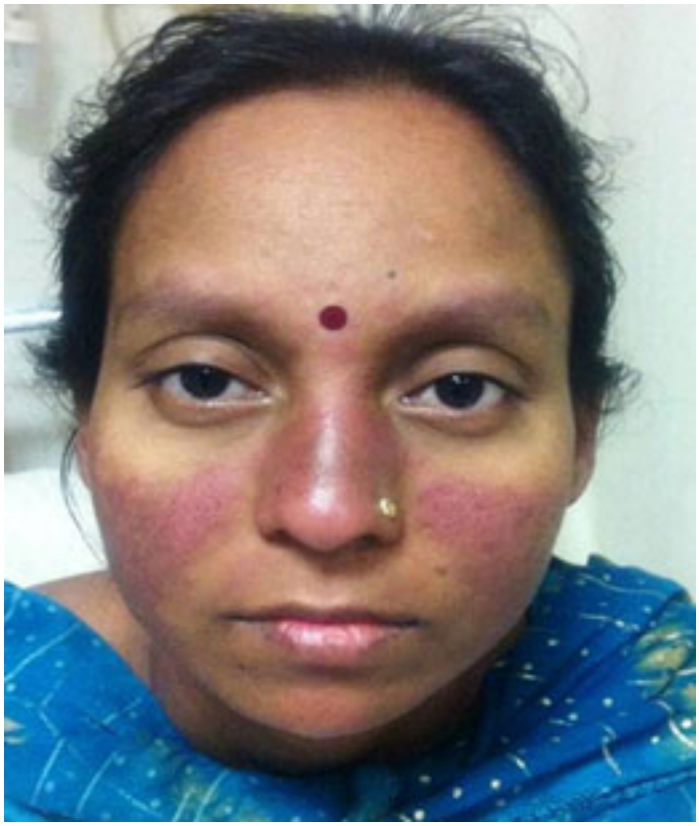

Figure 1: Malar rash: butterfly shape, flat, non-tender erythematosus rash over the cheek and nose

Kumar N et al. BMJ Case Reports. 2013;2013:bcr-2012-008101

Figure 2: a) Photograph of a face with skin rashes sparing the bridge of the nose and malar area. b) Photograph of a face showing asymmetric hyperpigmented, polycylic, and annular scaly plaques with scaling involving pre-auricular area and cheek

Rajasekharan C et al. BMJ Case Reports. 2013;2013:bcr-2012-007886

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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