Annals of Internal Medicine®

In the Clinic®

Systemic Lupus Erythematosus

Screening

Diagnosis

Treatment

Practice Improvement

Systemic lupus erythematosus (lupus) is characterized by aberrant activity of the immune system, leading to variable clinical symptoms. Lupus is more prevalent in African American women and women in other ethnic minority groups. Diagnosing, treating, and identifying novel therapies for lupus is challenging because of its genetic and phenotypic heterogeneity. Lupus nephritis is the most common target-organ manifestation and requires individualized care to minimize toxicity. A multidisciplinary approach to caring for pregnant patients with lupus is essential to optimize outcomes.

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1. Rees F, Doherty M, Grainge MJ, et al. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford). 2017;56:1945-61. [PMID: 28968809]
2. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2018;30:144-50. [PMID: 29251660]
3. Yen EY, Shaheen M, Woo JMP, et al. 46-year trends in systemic lupus erythematosus mortality in the United States, 1968 to 2013: a nationwide population-based study. Ann Intern Med. 2017; 167:777-85. [PMID: 29086801]
4. Lee YH, Choi SJ, Ji JD, et al. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus. 2016;25: 727-34. [PMID: 26811368]
5. Sestak AL, Fürnrohr BG, Harley JB, et al. The genetics of systemic lupus erythematosus and implications for targeted therapy. Ann Rheum Dis. 2011;70 Suppl 1:i37-43. [PMID: 21339217]
6. Omarjee O, Picard C, Frachette C, et al. Monogenic lupus: dissecting heterogeneity. Autoimmun Rev. 2019;18:102361. [PMID: 31401343]
7. Jeong DY, Lee SW, Park YH, et al. Genetic variation and systemic lupus erythematosus: a field synopsis and systematic meta-analysis. Autoimmun Rev. 2018;17:553-66. [PMID: 29635078]
8. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003;349:1526-33. [PMID: 14561795]
9. Seibold JR, Wechsler LR, Cammarata RJ. LE cells in intermittent hydrarthrosis [Letter]. Arthritis Rheum. 1980;23:958-9. [PMID: 6157396]
10. Ball EM, Bell AL. Lupus arthritis–do we have a clinically useful classification? Rheumatology (Oxford). 2012;51:771-9. [PMID: 22179731]
11. Vera-Recabarren MA, García-Carrasco M, Ramos-Casals M, et al. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus: clinical and immunological study of 270 patients. Br J Dermatol. 2010;162: 91-101. [PMID: 19785596]

Systemic lupus erythematosus (SLE, or lupus) is a condition in which the immune system attacks healthy cells and tissues throughout the body. Immune system activation in SLE is characterized by exaggerated B cell and T cell responses and loss of immune tolerance against self-antigens. Production and defective elimination of antibodies, circulation and tissue deposition of immune complexes, and complement and cytokine activation contribute to clinical manifestations that range from mild fatigue and joint pain to severe, life-threatening organ damage.

Recent data from lupus registries in the United States and published studies worldwide have allowed for more accurate estimates of the incidence and prevalence of SLE. The estimated incidence of 23.2 cases per 100 000 persons in North America is the highest worldwide (1). Lupus is more common in African Americans, Hispanics, and Asians than in whites (2).

Although SLE has no cure, it can be effectively managed with medications. A population-based study of SLE in the United States showed an overall decrease in age-standardized mortality rate of 24.4% over a 46-year period (3), likely due to treatment advances and earlier diagnosis. However, mortality is still approximately 2- to 3-fold higher in patients with SLE than in the general population, particularly in females, members of racial/ethnic minority groups, residents of the South or West, and persons aged 65 years or older. The most common causes of death in patients with SLE are renal disease, cardiovascular disease, and infection (3, 4).

Screening

Which patients are at elevated risk for lupus?

There is insufficient evidence to determine whether specific genetic factors increase risk for lupus. Early genetic studies, driven by the observation of familial SLE aggregation and high concordance in monozygotic twins, have implicated HLA and early complement component genes (5). Complement C1, C2, and C4 deficiencies, leading to defective clearance of nucleic acids, type I interferonopathies, and SLE-like syndromes due to mutations in some proapoptotic genes, are examples of monogenic lupus (6). Genome-wide association studies have identified at least 70 lupus susceptibility loci (7). The functional significance of these variants and their potential implication in the expression of lupus remain largely unknown. In addition, sex hormones and possibly environmental influences may contribute to immune system dysfunction in genetically predisposed persons.

Should clinicians screen asymptomatic patients if they are at increased risk?

Most experts do not recommend screening asymptomatic persons for lupus, even those with a family history of the disease. Antinuclear antibodies (ANA), especially of low titer, can be detected in healthy persons or in patients with other autoimmune or infectious diseases. Furthermore, serologic evidence of ANA, indicating an aberrant immune system activation, may precede the clinical manifestations of lupus by 3–9 years (8). No evidence suggests that treating to modulate the immune system during this clinically "silent" period can stop or delay lupus development.

Screening... Single-gene mutations causing SLE are rare. Although many gene variants have been linked to lupus, current evidence is insufficient to support screening for them. ANA testing in asymptomatic persons is not useful because immune reaction to nuclear antigens is not SLE-specific, can be detected in healthy persons, and may precede SLE manifestations by many years.

CLINICAL BOTTOM LINE

Diagnosis

What symptoms or physical examination findings should prompt clinicians to consider a diagnosis of lupus?

The initial presentation of lupus often mimics a viral syndrome. Constitutional symptoms, such as weight loss, fatigue, and low-grade fever, are common and may be accompanied by arthralgias or arthritis. Arthritis in lupus is characterized by prolonged morning stiffness and mild to moderate joint swelling. It is nonerosive, may be symmetrical or asymmetrical, and may affect large or small joints. Large effusions are not as common in lupus as in rheumatoid arthritis, and the synovial fluid is not as inflammatory (9). Similarly, joint deformities are not as common. Jaccoud arthropathy, which may include reducible ulnar deviation, swan neck deformities, or Z-shaped thumb, is present in 2.8%–4.3% of patients (10). When constitutional symptoms with arthralgias or arthritis are not accompanied by other characteristic manifestations of lupus, such as photosensitive rash on the face, neck, or extremities, it is appropriate to conduct a clinical and laboratory evaluation for infection before trying to establish a diagnosis of SLE.

Cutaneous manifestations are common and may occur in up to 75%–80% of patients (11). They are categorized as acute, subacute, chronic, and bullous lupus. Acute cutaneous lupus consists of indurated or flat erythematous lesions on the malar eminences, scalp, arms, hands, neck, and chest. The malar rash may be confused with rosacea, drug eruption, or polymorphous light eruption, but skin biopsy is rarely necessary when other clinical manifestations and serologic evidence consistent with SLE are present. Subacute cutaneous lupus consists of annular lesions that may coalesce into a polycyclic (overlapping ring-shaped) rash or papulosquamous lesions that do not scar and are distributed where light exposure is most frequent. It is often associated with anti-SSA antibodies. Chronic cutaneous lupus includes discoid lupus and other rare subsets, such as lupus panniculitis, hypertrophic lupus erythematosus (characterized by verrucous lesions), tumid lupus or lupus tumidus (smooth, shiny, red-violet plaques, usually on the head and neck), and chilblain lupus (purplish-blue lesions on the fingers, toes, or ears). Discoid lupus is the most common form of chronic cutaneous lupus and is characterized by indurated plaques that resolve with significant scarring and hypopigmentation. Although acute cutaneous lupus is nearly always associated with systemic lupus, discoid lupus is infrequently (3%–5%) associated with systemic disease.

12. Alarcón GS, Friedman AW, Straaton KV, et al. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. LUpus in MInority populations: NAture vs. Nurture. Lupus. 1999;8:197-209. [PMID: 10342712]
13. Vilá LM, Alarcón GS, McGwin G Jr, et al; Lumina Study Group. Systemic lupus erythematosus in a multiethnic US cohort, XXXVII: association of lymphopenia with clinical manifestations, serologic abnormalities, disease activity, and damage accrual. Arthritis Rheum. 2006;55:799-806. [PMID: 17013840]
14. Durán S, Apte M, Alarcón GS, et al; Lumina Study Group. Features associated with, and the impact of, hemolytic anemia in patients with systemic lupus erythematosus: LX, results from a multiethnic cohort. Arthritis Rheum. 2008;59:1332-40. [PMID: 18759263]
15. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825-35. [PMID: 27821390]
16. Zhang L, Lee G, Liu X, et al. Long-term outcomes of end-stage kidney disease for patients with lupus nephritis. Kidney Int. 2016;89:1337-45. [PMID: 27165824]
17. Cervera R, Khamashta MA, Font J, et al; European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82:299-308. [PMID: 14530779]
18. Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med. 2010;31:479-88. [PMID: 20692540]
19. Silpa-archa S, Lee JJ, Foster CS. Ocular manifestations in systemic lupus erythematosus. Br J Ophthalmol. 2016;100:135-41. [PMID: 25904124]
20. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677-86. [PMID: 22553077]

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21. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400-12. [PMID: 31385462]
22. van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis. 2012; 71:1343-9. [PMID: 22337213]
23. Doria A, Stohl W, Schwarting A, et al. Efficacy and safety of subcutaneous belimumab in anti-double-stranded DNA-positive, hypocomplementemic patients with systemic lupus erythematosus. Arthritis Rheumatol. 2018;70: 1256-64. [PMID: 29671280]
24. Chrisman OD, Snook GA, Wilson TC, et al. Prevention of venous thromboembolism by administration of hydroxychloroquine. A preliminary report. J Bone Joint Surg Am. 1976;58:918-20. [PMID: 789380]
25. Espinola RG, Pierangeli SS, Gharavi AE, et al. Hydroxychloroquine reverses platelet activation induced by human IgG antiphospholipid antibodies. Thromb Haemost. 2002;87:518-22. [PMID: 11916085]
26. Marmor MF, Kellner U, Lai TY, et al; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123: 1386-94. [PMID: 26992838]
27. Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. Rheumatology (Oxford). 2012;51:1145-53. [PMID: 22271756]
28. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26:1275-9. [PMID: 10381042]
29. Fortin PR, Abrahamowicz M, Ferland D, et al; Canadian Network For Improved Outcomes in Systemic Lupus. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2008;59:1796-804. [PMID: 19035431]

What other clinical manifestations should clinicians look for in potential cases?

Systemic lupus may present in many other ways. Although fever, rash, and arthritis are the classic initial symptoms, abrupt onset with target-organ involvement is also common, particularly in Hispanics (61%) and African Americans (45%) compared with whites (41%) (12). SLE should be considered when patients, particularly women of reproductive age, present with hematologic findings, such as thrombocytopenia, leukopenia, lymphopenia, or anemia; renal findings, such as hematuria, proteinuria, cellular casts, or elevated serum creatinine level; respiratory symptoms, such as cough, dyspnea, hemoptysis, or pleuritic pain; or central nervous system (CNS) signs, such as headache, photophobia, or focal neurologic deficits.

Hematologic manifestations

Cytopenias are common in patients with lupus, and moderate to severe lymphopenia is associated with high disease activity and organ damage (13). Hemolytic anemia is uncommon and is usually associated with disease onset, thrombocytopenia, and African American race (14).

Renal manifestations

Renal involvement is a common target-organ manifestation; it has a poor prognosis due to the high risk for organ failure. Up to 50% of patients with SLE have evidence of renal disease at presentation (15). Lupus end-stage kidney disease is associated with worse survival among dialysis and transplant patients compared with other causes of end-stage kidney disease (16). In a multicenter cohort of 1000 patients with SLE, those with lupus nephritis had lower 10-year survival than those with nonrenal disease (17).

Respiratory involvement

Primary or secondary involvement of the respiratory system may occur in lupus. Presenting symptoms and treatment response vary depending on the affected anatomical site. Pleuritis is the most common respiratory SLE manifestation, affecting 30%–50% of patients (18). Lupus pleuritis should be diagnosed only after exclusion of other causes of pleural effusion, such as infection, pulmonary embolism, liver disease, heart disease, and cancer. When significant pleural effusions are present, analysis of pleural fluid is warranted. Bronchoscopy for bacterial, mycobacterial, fungal, and viral cultures may also be indicated. Vascular involvement may cause diffuse alveolar hemorrhage, pulmonary hypertension, or thromboembolic disease. Parenchymal damage is less common and may be caused by interstitial lung disease, acute pneumonitis, or bronchiolitis obliterans with organizing pneumonia. Acute lupus pneumonitis is rare and carries a high mortality risk. Infection and pulmonary embolism must always be excluded in patients with suspected lupus pneumonitis, and caution is needed to avoid use of immunosuppression in patients with active infection.

Neuropsychiatric manifestations

Neuropsychiatric SLE manifestations may be caused by vasculopathy, autoantibodies, and inflammatory mediators and may include headache, aseptic meningitis, vasculitis, movement disorder, seizure disorder, cognitive dysfunction, psychosis, demyelinating disease, myelopathy, autonomic disorder, and peripheral neuropathy.

Ocular manifestations

Ocular manifestations include keratoconjuctivitis sicca (with or without Sjögren syndrome), keratitis, episcleritis, scleritis, uveitis,

retinal vasculitis, occlusion of the retinal artery or vein, retinopathy, and many other less common manifestations (19).

Gastrointestinal manifestations

Gastrointestinal symptoms may include anorexia, nausea, vomiting, abdominal pain, and diarrhea. Other causes of abdominal pain in lupus are mesenteric vasculitis and hepatobiliary disease. Rare gastrointestinal complications include intestinal pseudoobstruction, protein-losing enteropathy, and pancreatitis. Immunocompromised patients with lupus are also prone to enteritis from cytomegalovirus or salmonella infection.

What role do the American College of Rheumatology classification criteria play in diagnosis?

Lupus is a multiorgan disease that can mimic infectious diseases, cancer, and other autoimmune conditions. **Table 1** lists the 1997 American College of Rheumatology (ACR) classification criteria for SLE. These criteria facilitate a systematic approach to diagnosis by focusing on the most common clinical and laboratory manifestations of SLE, assuming that other diseases presenting with similar clinical or laboratory manifestations have been excluded. Four of the 11 criteria must be met for classification of systemic lupus. Although intended to assist in classification, the ACR criteria offer a highly sensitive and specific tool for diagnosing SLE, based on objective disease manifestations. However, patients with mild disease may be missed. In 2012, the Systemic Lupus International Collaborating Clinics revised the ACR classification criteria, increasing the sensitivity but not the specificity of detecting SLE compared with the 1997 ACR criteria (20). In 2019, the European League Against Rheuma-

30. Steinberg AD. The treatment of lupus nephritis. Kidney Int. 1986;30:769-87. [PMID: 3537464]
31. Austin HA 3rd, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986; 314:614-9. [PMID: 3511372]
32. Hochstadt A, Rozman Z, Zandman-Goddard G. [Mycophenolate mofetil as a novel treatment for lupus nephritis]. Harefuah. 2011;150: 542-7, 550. [PMID: 21800496]
33. Kamanamool N, McEvoy M, Attia J, et al. Efficacy and adverse events of mycophenolate mofetil versus cyclophosphamide for induction therapy of lupus nephritis: systematic review and meta-analysis. Medicine (Baltimore). 2010; 89:227-35. [PMID: 20616662]
34. Anderka MT, Lin AE, Abuelo DN, et al. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. Am J Med Genet A. 2009;149A: 1241-8. [PMID: 19441125]

Table 1. **1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus**

Criterion	*Definition*
Malar rash	Flat or raised erythema over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous raised patches or atrophic scarring (older lesions)
Photosensitivity	Rash as a result of reaction to sunlight
Oral ulcers	Usually painless oral or nasopharyngeal ulcerations observed by physician
Arthritis	Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness and swelling
Serositis	Pleuritis: Convincing history of pleuritic pain or rubbing heard by physician, or evidence of pleural effusion Pericarditis: Documented by electrocardiogram, or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/d or >3 on dipstick Cellular casts red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures (in the absence of offending drugs or metabolic derangement) Psychosis (in the absence of offending drugs or metabolic derangement)
Hematologic disorder	Hemolytic anemia: with reticulocytosis Leukopenia: <4000/mm on ≥2 occasions Lymphopenia: <1500/mm on ≥2 occasions Thrombocytopenia: <100 000/mm in the absence of offending drugs
Immunologic disorder	Anti–double-stranded DNA Anti-Smith antibodies Antiphospholipid antibodies based on abnormal serum level of IgG or IgM anticardiolipin antibodies, positive test result for lupus anticoagulant using a standard method, or false-positive serologic test result for syphilis known to be positive for ≥6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
Antinuclear antibody	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

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35. Hahn BH, McMahon MA, Wilkinson A, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808. [PMID: 22556106]
36. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971-80. [PMID: 14999109]
37. Houssiau FA, D'Cruz D, Sangle S, et al; MAINTAIN Nephritis Trial Group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69:2083-9. [PMID: 20833738]
38. Dooley MA, Jayne D, Ginzler EM, et al; ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886-95. [PMID: 22087680]
39. Tamirou F, D'Cruz D, Sangle S, et al; MAINTAIN Nephritis Trial Group. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. Ann Rheum Dis. 2016;75:526-31. [PMID: 25757867]
40. Moroni G, Doria A, Mosca M, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. Clin J Am Soc Nephrol. 2006;1:925-32. [PMID: 17699309]
41. Lee YH, Lee HS, Choi SJ, et al. Efficacy and safety of tacrolimus therapy for lupus nephritis: a systematic review of clinical trials. Lupus. 2011;20:636-40. [PMID: 21382917]
42. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75:30-6. [PMID: 25550339]
43. Kamanamool N, Ingsathit A, Rattanasiri S, et al. Comparison of disease activity between tacrolimus and mycophenolate mofetil in lupus nephritis: a randomized controlled trial. Lupus. 2018;27:647-56. [PMID: 29105558]

Box: Basic Investigations for SLE

Complete blood count

Direct Coombs test (indicated if patient presents with hemolytic anemia and reticulocytosis)

Comprehensive metabolic panel

Erythrocyte sedimentation rate

C-reactive protein

Urinalysis

Serologic tests (ANA and, if positive, anti-dsDNA, anti-SSA/SSB, anti-Smith/RNP antiphospholipid antibodies); negative ANA result is inconsistent with diagnosis of SLE

Complement C3 and C4

Creatine phosphokinase (indicated in patients presenting with muscle weakness)

ANA = antinuclear antibody; dsDNA = double-stranded DNA; SLE = systemic lupus erythematosus.

tism (EULAR) in collaboration with the ACR published updated criteria for classification of SLE, which include 10 domains and 22 criteria, each with weight varying from 2–10 (21). In addition to a positive ANA test result—a required entry criterion—a total weight of 10 is required to classify a syndrome as SLE (**Figure**). The 2019 EULAR/ACR criteria and their corresponding numerical weight add a layer of complexity in diagnosing SLE; therefore, their application is more pertinent to clinical trials or diagnosis of challenging cases.

What laboratory tests should clinicians use to support the diagnosis?

Clinicians should test for ANA, and if the result is positive, they should test for antigen-specific ANA, such as those targeting double-stranded DNA (dsDNA) or ribonucleoprotein complexes (Ro/SSA, La/SSB, Smith, and RNP), collectively referred to as *extractable nuclear antigens*. The specificity of anti-dsDNA antibodies for lupus is greater than 60%. Although anti-Smith antibodies are more than 90% specific for lupus, they are detected in only about 30% of patients with the disease. The initial laboratory evaluation to assess disease activity and target-organ involvement is described in the **Box:** Basic Investigations for SLE.

What other diagnoses should clinicians consider?

Chronic fatigue syndrome and fibromyalgia may present with diffuse musculoskeletal symptoms mimicking lupus. These syndromes may be primary in the absence of underlying autoimmune disease, or they may be secondary to autoimmune conditions, especially lupus. SLE can be excluded in the absence of inflammatory pain and negative serologic results. Rheumatoid arthritis is characterized by intensely inflammatory, erosive (when advanced) arthritis and positive results on rheumatoid factor or anti–cyclic citrullinated peptide antibody testing.

Such drugs as procainamide, hydralazine, minocycline, isoniazid, and tumor necrosis factor inhibitors can cause drug-induced lupus, a clinical syndrome resembling SLE that is characterized by fever, serositis, arthritis, and rash. Antihistone antibodies are detected in approximately 75% of patients with drug-induced lupus; however, they can also be present in SLE and are not pathognomonic. Anti-dsDNA, or antibodies to extractable nuclear antigens, are rare in drug-induced lupus, and symptoms usually abate within days or weeks after withdrawal of the inciting drug.

Small- or medium-vessel vasculitides, thrombotic thrombocytopenic purpura, and viral arthritis, as seen in parvovirus infection and

HIV/AIDS, can also mimic SLE; laboratory studies, viral serologic tests, and tissue histopathologic testing may help distinguish these conditions from SLE. Hematopoietic cancer and malignant lymphoproliferative syndromes may present with positive ANA results, anemia, low-grade fever, pleural effusions, and lymphadenopathy and can be misdiagnosed as lupus.

When should clinicians consider consulting a rheumatologist or another specialist?

Clinicians should consult a rheumatologist in all patients whose clinical manifestations and serologic studies suggest SLE. Evidence of renal, pulmonary, CNS, ocular, or gastrointestinal disease necessitates a coordinated, mul-

Figure. **European League Against Rheumatism/American College of Rheumatology classification criteria for SLE.**

Entry criterion: positive ANA test result

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

Additive criteria

- **Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on ≥1 occasion is sufficient.**
- **SLE classification requires ≥1 clinical criterion and ≥10 points.**
- **Criteria need not occur simultaneously.**
- **Within each domain, only the highest weighted criterion is counted toward the total score.**

Criteria	Weight
Clinical domains	
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g per 24 h	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10
Immunologic domains	
Antiphospholipid antibodies	
Anticardiolipin antibodies *or* anti-β2GP1 antibodies *or* lupus anticoagulant	2
Complement proteins	
Low C3 *or* low C4 level	3
Low C3 *and* low C4 level	4
SLE-specific antibodies	
Anti-dsDNA antibody* *or* anti-Smith antibody	6

Classify as SLE with a score of ≥10 if entry criterion is fulfilled.

Adapted from reference 21. ANA = antinuclear antibody; β2GP1 = β2 glycoprotein 1; dsDNA = double-stranded DNA; HEp-2 = human epithelial type 2; SLE = systemic lupus erythematosus.
* In an assay with 90% specificity against relevant disease controls.

44. Rovin BH, Furie R, Latinis K, et al; LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64:1215-26. [PMID: 22231479]
45. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab trial. Arthritis Rheum. 2010;62:222-33. [PMID: 20039413]
46. Andrade-Ortega L, Irazoque-Palazuelos F, López-Villanueva R, et al. [Efficacy of rituximab versus cyclophosphamide in lupus patients with severe manifestations. A randomized and multicenter study]. Reumatol Clin. 2010;6:250-5. [PMID: 21794725]
47. Tanaka Y, Takeuchi T, Miyasaka N, et al. Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy. Mod Rheumatol. 2016;26:80-6. [PMID: 26054418]
48. Iaccarino L, Bartoloni E, Carli L, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. Clin Exp Rheumatol. 2015;33:449-56. [PMID: 26053285]
49. Radhakrishnan J, Moutzouris DA, Ginzler EM, et al. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. Kidney Int. 2010;77:152-60. [PMID: 19890271]
50. Spetie DN, Tang Y, Rovin BH, et al. Mycophenolate therapy of SLE membranous nephropathy. Kidney Int. 2004;66:2411-5. [PMID: 15569333]
51. Jais X, Launay D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. Arthritis Rheum. 2008;58:521-31. [PMID: 18240255]

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tidisciplinary approach with the help of appropriate specialists. The goal of care is a timely, accurate diagnosis; effective treatment of acute disease; appropriate monitoring and dose adjustment; and early introduction of a steroid-sparing regimen.

Diagnosis... Lupus is a multisystem disease that often presents a diagnostic challenge because it can include cutaneous, renal, respiratory, cardiovascular, CNS, and gastrointestinal manifestations that characterize many other conditions. The ACR classification criteria can be used to guide the diagnosis of systemic lupus.

CLINICAL BOTTOM LINE

Treatment

What medications are used to treat lupus?

Clinicians use a broad range of medications to treat lupus, including glucocorticoids, antimalarial agents, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive agents, and B cell–targeting biologics (**Table 2**). Hydroxychloroquine is the cornerstone of SLE treatment.

Glucocorticoids are first-line agents for most SLE manifestations, with dosage and treatment duration based on clinical experience and consensus. The choice of immunosuppressive agent for treatment of lupus nephritis is based on histopathologic classifications.

Belimumab, a monoclonal antibody targeting the B-lymphocyte stimulator, has been shown to improve musculoskeletal and mucocutaneous manifestations and immunologic parameters in lupus, initially excluding renal and CNS disease (22). Recently, it has been shown that belimumab administered subcutaneously decreases SLE exacerbations, thus permitting tapering of corticosteroid doses (23). Collectively, accumulating evidence supports a role for B-lymphocyte stimulator inhibition in treating mild to moderate lupus and in providing steroid-sparing effect.

How should clinicians initiate therapy in a stable patient who is not having a flare?

Hydroxychloroquine or other antimalarial agents prevent disease exacerbations and should be prescribed to patients with SLE. In addition to preventing lupus exacerbations and reducing the risk for congenital heart block in neonatal SLE, hydroxychloroquine has antithrombotic effects secondary to inhibition of platelet adhesiveness, aggregation, and activation (24, 25) and is particularly important for treatment of patients with lupus with prothrombotic tendencies, including those with antiphospholipid antibodies or significant proteinuria. Hydroxychloroquine is generally well tolerated. In 2016, updated guidelines recommended a maximum daily dose of 5 mg/kg of body weight. A dose higher than the recommended dose, years of exposure to the medication, renal disease, and use of tamoxifen are the major risk factors for retinopathy (26). Skin pigmentation and rare cases of neuromuscular or cardiac toxicity have also been reported.

How should clinicians choose therapy for a patient who is having a flare?

Severe SLE manifestations, such as lupus nephritis, alveolar hemorrhage, or CNS vasculitis,

52. Broen JCA, van Laar JM. Mycophenolate mofetil, azathioprine and tacrolimus: mechanisms in rheumatology. Nat Rev Rheumatol. 2020;16:167-78. [PMID: 32055040]
53. Neumann R, Foster CS. Corticosteroid-sparing strategies in the treatment of retinal vasculitis in systemic lupus erythematosus. Retina. 1995;15:201-12. [PMID: 7569347]
54. Tseng CE, Buyon JP, Kim M, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:3623-32. [PMID: 17075807]
55. Mok CC, Ho LY, Fong LS, et al. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Ann Rheum Dis. 2013;72:659-64. [PMID: 22589375]
56. Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med. 2015;163:153-63. [PMID: 26098843]
57. Kostopoulou M, Nikolopoulos D, Parodis I, et al. Cardiovascular disease in systemic lupus erythematosus: recent data on epidemiology, risk factors and prevention. Curr Vasc Pharmacol. 2019. [PMID: 31880245]
58. Yazdany J, Trupin L, Tonner C, et al. Quality of care in systemic lupus erythematosus: application of quality measures to understand gaps in care. J Gen Intern Med. 2012;27:1326-33. [PMID: 22588825]
59. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017;69:1521-37. [PMID: 28585373]

should be treated with glucocorticoids administered intravenously in conjunction with immunosuppressive medications. Glucocorticoids can be gradually withdrawn once remission is achieved and an appropriate steroid-sparing agent is added if it is warranted. Oral prednisone or methylprednisolone is used for arthritis, pleuropericarditis, cutaneous vasculitis, and uveitis. Decisions about glucocorticoid dosage and treatment duration for specific manifestations currently rely largely on clinical experience because few clinical trials have been performed.

Significant overlap exists between the symptoms of lupus manifestations and some glucocorticoid complications, including avascular bone necrosis, myopathy, and psychosis.

Furthermore, despite the abundance of observational data on glucocorticoid toxicity, evidence from randomized controlled trials (RCTs) is limited (27). Daily doses of 5–7.5 mg are associated with relatively low risk for toxicity, although monitoring for Cushing syndrome, osteoporosis, cataract, glaucoma, hyperglycemia, and hypertension is justified. Prolonged treatment with medium to high doses carries a higher risk for complications, including myopathy, psychosis, hyperlipidemia, and atherosclerosis. The prevalence and incidence of these complications with different corticosteroid regimens are unclear.

How should clinicians choose drug therapy for cutaneous manifestations?

Commonly used topical treatments for all forms of cutaneous lupus (acute, subacute, and chronic) include tacrolimus, R-salbutamol pimecrolimus, clobetasol, betamethasone, or photoprotection. RCTs have demonstrated their efficacy as well as the efficacy of systemic hydroxychloroquine or chloroquine in cutaneous SLE. Although other immunosuppressive or biologic agents, such as methotrexate, mycophenolate mofetil, azathioprine, and rituximab, may be used for cutaneous lupus, evidence is based largely on case reports or prospective, nonrandomized studies. The current interest in biologics will likely lead to prospective RCTs examining their use for cutaneous and systemic lupus.

How should clinicians choose drug therapy for lupus arthritis?

Low-dose glucocorticoids and antimalarials are first-line agents

Table 2. **Drug Treatment for Systemic Lupus Erythematosus**

Agent	*Mechanism of Action*	*Dosage*	*Common Adverse Effects*
Nonsteroidal anti-inflammatory drugs	Anti-inflammatory	–	Gastritis, nephrotoxicity, fluid retention
Glucocorticoids	Anti-inflammatory effect due to negative transcriptional regulation of proinflammatory genes	Low: ≤7 mg/d Medium: >7–≤30 mg/d High: >30–≤100 mg/d Very high: >100 mg/d Pulse: ≥250 mg/d	Fluid retention, diabetes mellitus, hypertension, acne, myopathy, hyperlipidemia, psychosis, avascular bone necrosis, osteoporosis
Hydroxychloroquine	Immunomodulatory and antithrombotic effect	200–400 mg/d (orally)	Skin hyperpigmentation, retinal toxicity (rare), myopathy with peripheral neuropathy and cardiac myotoxicity (extremely rare)
Mycophenolate mofetil	Inhibits lymphocyte proliferation by inhibiting inosine monophosphate dehydrogenase and de novo synthesis of guanosine nucleotides; promotes apoptosis of T lymphocytes	Up to 3000 mg/d (orally)	Gastrointestinal intolerance, myelosuppression
Azathioprine	Metabolizes to 6-thioguanine and 6-methylmercaptopurine and inhibits DNA synthesis and cell proliferation	50–150 mg/d (orally)	Gastrointestinal intolerance, myelosuppression, hepatotoxicity
Methotrexate	Inhibits DNA synthesis and increases release of adenosine	5–25 mg/wk (orally or subcutaneously)	Gastrointestinal intolerance, hepatotoxicity
Cyclophosphamide	Alkylating agent; promotes DNA cross-linking and inhibits T- and B-lymphocyte proliferation	Based on body surface area and renal function (intravenous or oral administration)	Hair loss, gastrointestinal toxicity, myelosuppression, hemorrhagic cystitis, bladder cancer, gonadal suppression, infertility
Cyclosporine	Calcineurin inhibitor; inhibits T-lymphocyte proliferation and expression or activation of proinflammatory cytokines	2.5–4.5 mg/kg of body weight per day (orally)	Nephrotoxicity, interaction with allopurinol, hypertension, myelosuppression
Tacrolimus	Calcineurin inhibitor	2–3 mg/d (orally)	Nephrotoxicity, neurotoxicity, myocardial hypertrophy, hyperkalemia, infection, cancer
Belimumab	Targets B-lymphocyte stimulator, inhibits B-lymphocyte proliferation and activation	Three 10-mg/kg doses given intravenously at 2-wk intervals and then 10 mg/kg intravenously every month	Hypersensitivity reaction, gastrointestinal toxicity, myalgias, depression, migraine, infection
Rituximab	Depletes CD20-expressing B lymphocytes	Two 1000-mg doses given intravenously at 2-wk intervals; may be repeated every 6 mo	Infusion reaction, infection, progressive multifocal leukoencephalopathy (rare)

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for treating arthritis in lupus. Methotrexate is often used for arthritis or cutaneous disease, particularly in patients without other systemic manifestations (28, 29). Methotrexate antagonizes folic acid and inhibits purine and pyrimidine synthesis, and it also increases extracellular adenosine release. Adenosine seems to be an important mediator of the anti-inflammatory effect of methotrexate.

How should clinicians choose and dose drug therapy for lupus nephritis?

Treatment of lupus nephritis is guided by histopathologic findings from kidney biopsy. The indications for kidney biopsy are presented in the **Box:** Indications for Kidney Biopsy in Patients With SLE; the currently accepted classification system for biopsy results is described in the **Box:** Histopathologic Classification of Lupus Nephritis.

Induction therapy

Class I or II lupus nephritis does not require immunosuppressive therapy, whereas class III or IV lupus nephritis is treated aggressively (**Table 3**). Seminal clinical trials on lupus nephritis established the combination of cyclophosphamide with intravenous glucocorticoids as standard induction therapy for class III and IV lupus nephritis (30, 31). Cyclophosphamide is an alkylating agent that promotes DNA cross-linking and affects T-cell and B-cell proliferation and antibody production. It is usually dosed according to total body surface area and adjusted for decreased creatinine clearance. Cyclophosphamide toxicity includes hematologic, infectious, urologic, reproductive, and rare pulmonary complications and bladder, skin, myeloproliferative, and oropharyngeal cancers. To date, there is no definitive evidence from clinical trials to guide clinicians on the dose of glucocorticoids for induction therapy of lupus nephritis. ACR recommendations are based on expert opinion and consensus.

Over the past decade, studies have also shown efficacy of mycophenolate mofetil for induction therapy in lupus nephritis (32) without establishing its superiority compared with cyclophosphamide (33). Mycophenolate mofetil is metabolized to mycophenolic acid, an inhibitor of inosine 5-monophosphate dehydrogenase, which is required for de novo synthesis of guanosine nucleotides. It inhibits lymphocyte proliferation, induces apoptosis of activated T cells, and inhibits adhesion molecule expression and fibroblast proliferation. Gastrointestinal toxicity is common and may respond to dose reduction or enteric-coated formulation. Hematologic toxicity is also common, ranging from mild cytopenias to red cell aplasia. Mycophenolate mofetil is contraindicated in pregnancy because of case reports suggesting teratogenicity (34).

The 2012 ACR guidelines on management of lupus nephritis recommend using either cyclophosphamide or mycophenolate mofetil combined with glucocorticoids for induction therapy of class III or IV proliferative lupus nephritis (35). Response to cyclophosphamide or mycophenolate mofetil may differ on the basis of race or ethnicity. Asians and Europeans may respond better to cyclophosphamide than Hispanics and African Americans (35).

Maintenance therapy

The ACR guidelines recommend either mycophenolate mofetil or azathioprine for maintenance therapy in lupus nephritis. Both are superior to cyclophosphamide for this purpose (36). Evidence from 2 studies of comparative efficacy of mycophenolate mofetil versus azathioprine was initially conflicting. The MAINTAIN Nephritis trial showed significant superiority of mycophenolate mofetil over azathioprine with respect to time to treatment failure, time to renal flare, and time to rescue therapy (37). In contrast, an open-label study of mycophenolate mofetil versus azathioprine for maintenance treatment of lupus nephritis showed no significant difference between groups in these outcomes over 4 years (38). Similarly, long-term follow-up data from the first trial did not support superiority of mycophenolate mofetil versus azathioprine (39).

Box: Histopathologic Classification of Lupus Nephritis

Class I: minimal mesangial

Class II: mesangial proliferative

Class III: focal proliferative

Class IV: diffuse proliferative (with active, active and chronic, or chronic lesions)

Class V: membranous (with or without coexisting class III or IV lupus nephritis)

Class VI: advanced sclerosing lupus nephritis with >90% globally sclerotic glomeruli

Box: Indications for Kidney Biopsy in Patients With SLE*

- Increasing serum creatinine level without compelling alternative causes
- Confirmed proteinuria ≥1.0 g per 24 h (either 24-h urine specimens or spot protein–creatinine ratio)
- Combination of the following: proteinuria ≥0.5 g per 24 h plus hematuria (≥5 erythrocytes per high-power field) or proteinuria ≥0.5 g per 24 h plus cellular casts

SLE = systemic lupus erythematosus.

** From reference 35.*

Calcineurin inhibitors, such as cyclosporine, may be an alternative for maintenance therapy. A multicenter randomized trial showed that cyclosporine and azathioprine are equally effective for maintenance treatment of lupus nephritis class IV and V and have similar effects on blood pressure and renal function (40).

Tacrolimus, also a calcineurin inhibitor, may be used to treat diffuse proliferative or membranous lupus nephritis. Meta-analysis of data from open-label trials, case–control studies, and RCTs showed that tacrolimus may be effective as induction and maintenance therapy for lupus nephritis or in treatment of refractory lupus nephritis with persistent proteinuria (41). In an open-label, randomized, controlled, parallel-group study of lupus nephritis class III to V, tacrolimus or mycophenolate mofetil combined with prednisolone showed similar efficacy in remission induction. With subsequent maintenance therapy with azathioprine for 5 years, the tacrolimus group demonstrated a nonsignificant trend of higher incidence of renal flares and decline in renal function (42). A more recent clinical trial also showed similar efficacy of tacrolimus and mycophenolate mofetil in induction therapy of lupus nephritis class III to V, with the mycophenolate mofetil regimen achieving lower disease activity during the maintenance period (43).

A prospective, multicenter, open-label, parallel RCT compared tacrolimus with mycophenolate mofetil for induction and maintenance therapy in lupus nephritis class III to V. All patients received prednisolone (0.7–1.0 mg/kg per day for 4 weeks and then tapered) and were randomly assigned to receive either tacrolimus (0.1 mg/kg per day) or mycophenolate mofetil (1.5–2 g/d) as induction therapy for 6 months. All patients who had achieved remission received azathioprine, 1–2 mg/kg per day, in the maintenance phase. Disease activity remission rate and time to disease activity remission were similar between groups (28.57% in the mycophenolate mofetil group and 24.39% in the tacrolimus group). In terms of disease activity (measured by the SLEDAI-2K [Systemic Lupus Erythematosus Disease Activity Index 2000]), tacrolimus was similar to mycophenolate mofetil during induction, but mycophenolate mofetil was more effective at 12 months (43).

Rituximab is a monoclonal antibody directed against CD20, a B-cell membrane protein. Rituximab depletes B cells from the peripheral blood. Open-label trials suggested that improvement of lupus nephritis occurred after B-cell depletion, but RCTs did not show statistically significant response compared with placebo (44–46). Nonetheless, small clinical trials in Japan (47) and Italy (48) support a role for rituximab in refractory lupus nephritis.

In summary, current ACR guidelines propose cyclophosphamide or mycophenolate mofetil in combination with corticosteroids for induction therapy and mycophenolate mofetil or azathioprine as preferred maintenance therapy for proliferative lupus nephritis. However, emerging data underscore a role for calcineurin inhibitors in treating class III or IV lupus nephritis and for rituximab com-

Table 3. **American College of Rheumatology Recommendations for Lupus Nephritis Treatment***

Disease Class	*Treatment*		
	First Step	*Second Step*	*Third Step*
Class I or II	No immunosuppressive treatment		
Class III or IV: Preferred treatment in African Americans and Hispanics	MMF + GC IV pulse, then prednisone, 0.5–1 mg/kg of body weight per day	If improved: MMF or AZA with or without low-dose daily GC If not improved: CYC (low or high dose†) + GC IV pulse, then daily GC	– If improved: MMF or AZA with or without low-dose daily GC If not improved: Rituximab or calcineurin inhibitors + GC
Class III or IV: Preferred treatment in whites with a European background	CYC (low or high dose†) + GC IV pulse, then prednisone, 0.5–1 mg/kg per day	If improved: MMF or AZA with or without low-dose daily GC If not improved: MMF + GC IV pulse, then daily GC	– If improved: MMF or AZA with or without low-dose daily GC If not improved: Rituximab or calcineurin inhibitors + GC
Class V	MMF, 2–3 g/d for 6 mo, plus prednisone, 0.5 mg/kg per day for 6 mo	If not improved: CYC, 500–1000 mg/m^2 BSA IV monthly × 6, plus GC IV pulse, followed by prednisone, 0.5–1 mg/kg per day	If improved: MMF, 1–2 g/d, or AZA, 2 mg/kg per day
Class VI	Preparation for renal replacement therapy		

AZA = azathioprine; BSA = body surface area; CYC = cyclophosphamide; GC = glucocorticoids; IV = intravenously; MMF = mycophenolate mofetil.
** Adapted from reference 35.*
† Low dose is 500 mg IV every 2 wk × 6 followed by maintenance therapy with oral MMF or AZA (regimen for whites of European background). High dose is 500–1000 mg/m^2 BSA IV every month × 6.

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bined with glucocorticoids in patients with inadequate response to cyclophosphamide or mycophenolate mofetil.

How should clinicians choose drug therapy for membranous nephritis?

Pure membranous nephritis is not associated with endocapillary proliferation and presents with variable degrees of proteinuria. The progression of renal dysfunction is slow compared with that of class III or IV lupus nephritis. The evidence to guide treatment of membranous lupus nephritis is limited (49, 50). ACR guidelines recommend mycophenolate mofetil for management of membranous lupus nephritis. Tacrolimus and azathioprine have also been studied for induction or maintenance treatment.

How should clinicians choose therapy for neuropsychiatric lupus?

Treatment of serious neuropsychiatric SLE manifestations, such as acute cerebrovascular manifestations, seizures, and aseptic meningitis, is empirical and includes intravenous glucocorticoids, immunoglobulin, and cyclophosphamide. Case reports and small, uncontrolled studies suggest a beneficial effect of rituximab in treatment of neuropsychiatric lupus; however, the relapse rate seems to be high.

Cerebrovascular manifestations of neuropsychiatric SLE with overlapping features of antiphospholipid antibody syndrome may warrant systemic anticoagulation in addition to immunosuppression.

How should clinicians choose therapy for respiratory manifestations?

Pleuritis responds to treatment with NSAIDs and low to moderate doses of glucocorticoids. Immunosuppressive treatment is reserved for refractory cases. Diffuse alveolar hemorrhage presents abruptly, carries a poor prognosis, and requires treatment with intravenous glucocorticoids and immunosuppressants. Plasmapheresis may also be considered. Pulmonary hypertension is rare in SLE (0.5%–17%) and may be secondary to vasculopathy, interstitial pulmonary fibrosis, or in situ thrombosis. Patients with SLE and pulmonary hypertension are at high risk for cardiac failure and early death. Endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogues with or without immunosuppressive medications may be used to treat pulmonary hypertension in lupus. A retrospective study showed that patients with SLE and mild to moderate pulmonary hypertension may respond to treatment with cyclophosphamide and glucocorticoids, whereas patients with more severe disease may require a combination of vasodilators and immunosuppressants (51).

Larger clinical trials in patients with lupus and pulmonary hypertension or interstitial lung disease have not been done, and treatment decisions are based on clinical experience. Mycophenolate mofetil and tacrolimus are emerging therapies for interstitial lung disease in connective tissue disorders (52). Acute lupus pneumonitis requires treatment with high doses of glucocorticoids and cyclophosphamide.

How should clinicians choose therapy for ocular manifestations?

Depending on the severity of the ocular involvement and the activity of the systemic disease, treatment may include topical steroid solutions, intraocular steroids, antimalarial agents, NSAIDs, or oral or intravenous glucocorticoids. Scleral or retinal involvement may require concomitant use of pulse glucocorticoids, followed by 1 mg/kg of prednisone equivalent, combined with immunosuppressive therapy (53). Retinal vasculitis and arterial or venous retinal occlusion in the presence of antiphospholipid antibodies may require concomitant use of immunosuppressive medications and antiplatelet agents or anticoagulation.

How should clinicians monitor patients who are being treated for lupus?

Laboratory testing should include a complete blood count, basic metabolic panel, and urinalysis on routine follow-up visits. These tests allow the clinician to evaluate for hematologic, renal, and other target-organ manifestations. Many clinicians also routinely test for dsDNA antibodies and complement C3 and C4 levels; however, this practice is controversial for clinically stable patients. Although a prospective RCT showed that 4 weeks of treatment with prednisone in clinically stable but serologically active patients averts severe flares (54), C3 and C4 and dsDNA antibodies are more useful in assessing SLE activity in symptomatic patients or in assessing treatment response. Other monitoring should be tailored to individual disease manifestations. Consideration should be given to laboratory monitoring for medication toxicity and ophthalmologic evaluation of patients treated with hydroxychloroquine. Clinicians should be alert to osteoporosis prevention and should prescribe treatment when appropriate. Clinicians should also consider periodic lipid testing and order lipid-lowering agents as needed.

Should people with lupus receive immunizations?

All patients with SLE should receive influenza and pneumococ-

cal vaccinations. In addition, the quadrivalent human papillomavirus vaccine is well tolerated and reasonably effective in patients with stable SLE and does not increase lupus activity or flares (55). Patients not receiving immunosuppressive therapy should receive herpes zoster vaccine according to established guidelines. Patients receiving immunosuppressive therapy or daily prednisone at a dose above 20 mg should not receive live attenuated vaccines, including herpes zoster vaccine, live attenuated influenza vaccine, measles-mumps-rubella vaccine, and smallpox vaccine. Tuberculin skin testing, or interferon-γ release assay, is recommended for patients with SLE requiring prolonged treatment with glucocorticoids or immunosuppressive therapy.

Are there risks for obstetric complications or adverse pregnancy outcomes?

Pregnancies in patients with lupus are considered high-risk and should be managed by a multidisciplinary team that includes a rheumatologist and a maternal-fetal medicine specialist. Patients with lupus may have flares during pregnancy and, compared with the general population, they have a higher risk for complications, such as preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, pregnancy loss, fetal growth retardation, and preterm birth. Several risk factors for adverse pregnancy outcomes have been identified, including lupus anticoagulant, antihypertensive use, Physician Global Assessment score greater than 1, and low platelet count. Maternal flares, higher disease activity, and smaller increases in C3 level later in pregnancy also predicted adverse pregnancy outcomes (56).

Ideally, pregnancy should be planned for periods of clinical remission. Preconception counseling along with effective and safe contraception and risk stratification are essential.

How should clinicians modify treatment for pregnant patients?

Use of antimalarials is safe during pregnancy and should be continued. Hydroxychloroquine improves maternal and fetal outcomes and reduces risk for congenital heart block and for thrombosis due to antiphospholipid antibodies. Other medications that are considered safe or acceptable in pregnancy include chloroquine, nonfluorinated glucocorticoids (such as prednisone, prednisolone, and methylprednisolone), azathioprine, cyclosporine, tacrolimus, and intravenous immunoglobulins.

Data are insufficient regarding the safety of belimumab in pregnancy. Dandy–Walker syndrome and Ebstein anomaly have been observed in infants of patients exposed to belimumab. Even though a causal relationship has not been established, belimumab should be avoided during pregnancy until clinical studies demonstrate its safety. Mycophenolate mofetil, methotrexate, and cyclophosphamide are contraindicated in pregnancy because of their teratogenicity, and use of these drugs should be discontinued at least 3–6 months before conception. Leflunomide is also contraindicated because of a lack of safety data. Because of its long half-life, a washout period with cholestyramine is recommended before conception.

Other nonimmunosuppressant medications used in pregnant patients with lupus are low-dose aspirin and low-molecular-weight heparin. Low-dose aspirin has been found to decrease risk for preeclampsia and should be started by the 12th week of gestation, especially in patients who are positive for antiphospholipid antibodies. Low-molecular-weight heparin is recommended for pregnant patients with lupus and an established diagnosis of antiphospholipid syndrome; prophylactic treatment may be extended in the immediate postpartum period. In patients with anti-SSA antibodies, fetal echocardiography should be performed serially between weeks 16 and 28 of gestation to detect conduction abnormalities or congenital heart block.

When should patients be hospitalized?

Patients with serious complications should be hospitalized. Indications include severe thrombocytopenia, severe or rapidly progressive renal disease, suspected lupus pneumonitis or pulmonary hemorrhage, and severe cardiovascular or CNS manifestations. A major cause of death in SLE is infection, including from opportunistic pathogens. Patients with SLE who have unexplained fever should be hospitalized for evaluation and initiation of treatment with antibiotics. Empirical coverage should include *Staphylococcus aureus*, *Pseudomonas* species, *Klebsiella* species, *Escherichia coli*, and *Acinetobacter* species. Chest pain in patients with lupus could be due to coronary artery disease, serositis, pulmonary embolism, or esophageal disease. Lupus increases risk for endothelial dysfunction, and long-term treatment with steroids increases traditional risk factors for coronary artery disease (57). Neurologic symptoms in pa-

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tients with lupus may be due to neuropsychiatric lupus, infection, coexisting antiphospholipid antibody syndrome, or hypertension. All patients with lupus who have acute neurologic manifestations should be admitted and rapidly evaluated with appropriate imaging, cerebrovascular fluid analysis, echocardiography, and laboratory studies.

Treatment... Hydroxychloroquine prevents disease flares and is the cornerstone of SLE treatment. Glucocorticoids are first-line agents for most SLE manifestations, with dosage and treatment duration based on clinical experience and consensus. Immunosuppressive treatment in lupus nephritis is based on histopathologic classifications. Treatment of other lupus manifestations is based on sparse evidence from clinical trials and clinical experience and often requires immunosuppressive therapy and a multidisciplinary approach.

CLINICAL BOTTOM LINE

Practice Improvement

Disease burden and significant long-term functional limitations in SLE may have substantial socioeconomic impact. Unlike other chronic diseases, such as diabetes mellitus or rheumatoid arthritis, there are no established models of care for SLE and tools for assessment of quality of care. Studies have shown discordant care for screening and management of vitamin D deficiency, hypertension, and management of cardiovascular risk factors in lupus (58). The overall categories where primary care can affect outcomes in lupus include immunizations; counseling on sun avoidance; management of hypertension, especially in patients with renal involvement; osteoporosis screening and prevention; identification, management, and counseling on cardiovascular risk factors; and cancer screening. An evidence-based model of quality of care in SLE is needed to ensure optimal disease outcomes and to minimize long-term disease burden.

What do professional organizations recommend regarding diagnosis and management?

In 2013, the ACR published guidelines for screening, treatment, and management of lupus nephritis (35). These guidelines are currently under review, and updates are anticipated in 2021. Particularly relevant to patients with lupus are the updated guidelines on prevention and management of glucocorticoid-induced osteoporosis published by the ACR in 2017; these include specific references to women of childbearing age (59). Finally, the ACR and EULAR jointly published new criteria for diagnosis of lupus in 2019 (21).

In the Clinic
Tool Kit

Systemic Lupus Erythematosus

Patient Information

www.niams.nih.gov/health-topics/lupus

www.niams.nih.gov/es/informacion-de-salud/lupus
Resources for patients on systemic lupus erythematosus in English and Spanish from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

https://medlineplus.gov/ency/article/000435.htm

https://medlineplus.gov/spanish/ency/article/000435.htm
Patient information on systemic lupus erythematosus in English and Spanish from the National Institutes of Health's MedlinePlus.

www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Lupus

www.rheumatology.org/I-Am-A/Patient-Caregiver/Enfermedades-y-Condiciones/Lupus-Espanol
Patient fact sheets on lupus in English and Spanish from the American College of Rheumatology.

Information for Health Professionals

www.rheumatology.org/Portals/0/Files/Classification-Criteria-Systemic-Lupus-Erythematosus.pdf
European League Against Rheumatism/American College of Rheumatology 2019 classification criteria for systemic lupus erythematosus.

www.aafp.org/afp/2016/0815/p284.html
Guidelines on the primary care approach to diagnosis and management of systematic lupus erythematosus from the American Academy of Family Physicians.

www.rheumatology.org/Portals/0/Files/Reproductive-Health-Guideline-Early-View-2020.pdf
American College of Rheumatology 2020 guideline for management of reproductive health in rheumatic and musculoskeletal diseases.

www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf
American College of Rheumatology 2017 guideline on prevention and treatment of glucocorticoid-induced osteoporosis.

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WHAT YOU SHOULD KNOW ABOUT SYSTEMIC LUPUS ERYTHEMATOSUS

What Is Systemic Lupus Erythematosus?

Systemic lupus erythematosus, also known as SLE or lupus, is a chronic disease in which the body's immune system attacks its own healthy cells and tissues. Lupus can cause fatigue, joint pain, rashes, and even life-threatening organ damage. Although there is no cure, symptoms and disease progression can be managed with medication and a multidisciplinary team approach.

Am I at Risk?

Lupus occurs more often in women than in men and is more common in African Americans, Hispanics, and Asians. Lupus usually starts when people are in their 20s and 30s.

What Are the Symptoms?

Symptoms of lupus can come and go. When symptoms are active, this is called a "flare." Symptoms can be mild or serious and may include:

- Feeling tired
- Painful and swollen joints
- Fever
- Rashes, particularly a butterfly-shaped rash over the cheeks or a red rash with raised round or oval patches
- Sores in the mouth or nose
- Chest pain when breathing deeply
- Sensitivity to sun or light

How Is It Diagnosed?

Lupus can be hard to diagnose because the symptoms are similar to those of many other medical conditions. You should not be tested if you do not have symptoms. There is no one test to diagnose lupus, so you will need a thorough history and physical examination combined with testing.

- Your doctor will ask you questions about your symptoms and medical history.
- You will have a physical examination.
- You will have blood and urine tests.
- If your doctor believes you have lupus, you might be referred to a rheumatologist. This is a doctor who specializes in autoimmune conditions.

How Is It Treated?

There is no cure for lupus, but the good news is that the symptoms and disease progression can be managed with medication. Treatment is based on your symptoms and the severity of the disease.

- Medicines like ibuprofen or steroids can be used to reduce swelling and pain.
- Antimalarial medicines may be used to help with tiredness, joint pain, and mouth sores.
- Medicines that control an overactive immune system can also help if others haven't worked. Be sure to ask about the benefits and side effects of these medicines before taking them.

Questions for My Doctor

- What can cause lupus symptoms to flare?
- How will my symptoms change over time?
- What medicines are best for me?
- What are the side effects of the medicines?
- How often should I be seen for follow-up?
- Do I need to see any other doctors?
- Will my lupus ever go away?
- Does lupus put me at risk for any other conditions?
- If I am pregnant or want to become pregnant, what things should I consider?

For More Information

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MedlinePlus
https://medlineplus.gov/lupus.html

Lupus Foundation of America
www.lupus.org

Patient Information

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