In the Clinic

Systemic Lupus Erythematosus

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CME Objective: To review current evidence for the screening, diagnosis, and treatment of systemic lupus erythematosus.

The information contained herein should never be used as a substitute for clinical judgment.

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Systemic lupus erythematosus (SLE, 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.

Because the symptoms of SLE vary widely and the condition often goes undiagnosed, it is unclear how many people in the United States have the disease. It is diagnosed 9 times more often in women than in men, which implies pathogenic mechanisms more prevalent in women. These mechanisms, which probably involve effects of sex chromosomes, specific genes, and hormones, have not been completely elucidated. SLE is more common and more severe in African American women, Hispanic women, and those of other ethnic minorities (1).

Although there is no cure for SLE, it can be effectively managed with medications; however, mortality is higher in patients with SLE than in the general population. The overall standardized mortality ratio (SMR) (ratio of deaths observed to deaths expected for an age group) for SLE is 2.4. Higher risk for death is associated with female sex, younger age, shorter SLE duration, and African American race (2).

Screening

Which patients are at elevated risk for lupus?

Evidence to determine whether people may be at risk for lupus because of specific genes is insufficient. Early genetic studies, driven by the observation of familial aggregation and high concordance in monozygotic twins, have implicated genes for HLA and early complement components (3). A few rare, single-gene risk factors have been linked to SLE. For example, C1, C2, or C4 genetic deficiencies can cause lupus but account for just 1–2% of cases (3). Recent genome-wide association studies have linked more than 30 gene polymorphisms to lupus (4). However, the functional significance of these variants and their potential implication to SLE pathogenesis remain largely unknown. In addition, sex chromosome genes, and possibly sex hormones and environmental influences, may contribute to immune system dysfunction in genetically predisposed individuals.

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

Most experts do not recommend screening asymptomatic persons for lupus, even those with a family history. Nevertheless, the immunologic test for antinuclear antibody (ANA) is often used for SLE screening even though it produces many false-positive results. ANA is detected in 3–5% of healthy individuals or patients with other autoimmune or infectious diseases. Furthermore, serologic evidence of ANAs, which indicates immune system activation, may precede the clinical manifestations required for diagnosis by 3 to 9 years (5). No evidence suggests that treating to modulate the immune system during this clinically "silent" period can stop or delay lupus development.

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Screening... Single-gene mutations causing SLE are rare. Although numerous gene variants have been linked to lupus, current evidence is insufficient to support screening for these variants. ANA testing in asymptomatic persons is not useful because immune reaction to nuclear antigens is not SLE-specific, can be detected in healthy individuals, 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. Such constitutional symptoms 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 symmetric or asymmetric, 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 (6). Joint deformities are not frequent in lupus. Jaccoud arthropathy, which may include reducible ulnar deviation, swan neck deformities, or z-shaped thumb, is present in 2.8–4.3% of patients (7). When constitutional symptoms with arthralgias or arthritis are not accompanied by other characteristic manifestations of lupus, such as photosensitive skin 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 70% of patients (8). They are categorized as acute, subacute, or chronic. 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 the chronic cutaneous disease and is characterized by scarring indurated plaques that resolve with significant depigmentation. Although acute cutaneous lupus is nearly always associated with systemic lupus, discoid lupus is infrequently (3–5%) associated with systemic disease (9).

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

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 quite common, particularly in

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Hispanics (61%) and African Americans (45%), as compared with white patients (41%) (10). SLE should be considered when patients, particularly women of reproductive age, present with hematologic, renal, respiratory, or central nervous system (CNS) manifestations, especially hematologic findings, such as thrombocytopenia, leukopenia, lymphopenia, or anemia; renal findings, such as hematuria, proteinuria, cellular casts, or elevated serum creatinine; respiratory symptoms, such as cough, dyspnea, hemoptysis, or pleuritic pain; or 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 (11). Hemolytic anemia is uncommon and usually associated with disease onset, thrombocytopenia, and African American ethnicity (12).

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 SLE patients have some evidence of renal disease at presentation (13). SLE nephritis is associated with a worse prognosis for 10-year survival than the nonrenal disease (14). Compared with the general population, life expectancy is reduced by 12.4, 15.1, and 23.7 years in lupus patients, those with renal disease, and those with renal damage, respectively (15).

Respiratory involvement

Involvement of the respiratory system may be primary or secondary. Presenting symptoms and the response to treatment vary, depending on the affected anatomical site. Pleuritis is the most common respiratory SLE manifestation, affecting 30–50% of patients (16). Lupus pleuritis should be diagnosed only after an analysis of pleural fluid and an evaluation for other causes of pleural effusion, such as infection, pulmonary embolism, liver disease, heart disease, and cancer. Bronchoscopy for bacterial, mycobacterial, fungal, and viral cultures may be indicated. Vascular involvement may cause diffuse alveolar hemorrhage, pulmonary hypertension, or thromboembolic disease. Parenchymal damage is less common and may be the result of 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.

Neuropsychiatric manifestations

Neuropsychiatric SLE manifestations may be caused by vasculopathy, autoantibodies, and inflammatory mediators and 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 the Sjogren syndrome), keratitis, episcleritis, scleritis, uveitis, retinal vasculitis, occlusion of the retinal artery or vein, retinopathy, and numerous other less common manifestations (17).

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 pseudo-obstruction, protein-losing enteropathy, and

pancreatitis. Immunocompromised lupus patients are also prone to enteritis from cytomegalovirus or salmonella infection.

Lupus is a multiorgan disease that can mimic infectious diseases, cancer, and other autoimmune conditions. Table 1 lists the American College of Rheumatology (ACR) classification criteria for SLE (18). These criteria facilitate a systematic approach to diagnosis by focusing on the most common SLE manifestations. Four of the 11 criteria are required 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 (19).

What laboratory tests should clinicians use to diagnose lupus?

Clinicians should test for ANA, and if the result is positive, follow-up testing for antigen-specific ANAs, such as those targeting double-stranded DNA (dsDNA) or ribonucleoprotein complexes (Ro/SSA, La/SSB, Smith, and

Table 1. American College of Rheumatology Classification Criteria for SLE*

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	Skin rash as a result of unusual reaction to sunlight
Oral ulcers	Usually painless oral or nasopharyngeal ulcerations, observed by physician
Arthritis	Nonerosive arthritis, involving 2 or more 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 or more occasions Lymphopenia: <1500/mm on 2 or more occasions Thrombocytopenia: <100 000/mm in the absence of offending drugs
Immunologic disorder	Anti-DsDNA Anti-Smith antibodies Antiphospholipid antibodies based on an 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 at least 6 mo and confirmed as false-positive by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
Antinuclear antibody	Detected by immunofluoresence (or equivalent assay) in the absence of drugs known to be associated with drug-induced SLE

**From reference 18.*

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Basic Investigations for SLE

- Complete blood count
- Direct Coombs test (indicated if patients present with hemolytic anemia and reticulocytosis)
- Comprehensive metabolic panel
- Erythrocyte sedimentation rate
- C-reactive protein
- Urinalysis
- Serologic testing (ANA and if positive, anti-DsDNA, anti-SSA/SSB, anti-Smith/RNP antiphospholipid antibodies); a negative ANA test is inconsistent with the diagnosis of SLE
- Complement C3 and C4
- Creatine phosphokinase (indicated in patients presenting with muscle weakness)

RNP, which are collectively referred to as extractable nuclear antigens) should be done. The specificity of anti ds-DNA antibodies for lupus is >60%. Anti-Smith antibodies are >90% specific for lupus; however, they are detected in only about 30% of lupus patients. 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?

The chronic fatigue syndrome and fibromyalgia may present with diffuse musculoskeletal symptoms mimicking lupus, or may be secondary to SLE. SLE can be excluded in the absence of inflammatory pain and negative results on serologic evaluation. Rheumatoid arthritis is characterized by symmetric, intensely inflammatory, erosive arthritis (when advanced) and positive results on rheumatoid factor or anti-CCP antibody testing.

Such drugs as procainamide, hydralazine, minocycline, isoniazide, and tumor necrosis factor inhibitors can cause drug-induced lupus, a clinical syndrome resembling SLE characterized by fever, serositis, arthritis, and rash. Antihistone antibodies are detected in approximately 75% of patients; however, they can also be seen 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 drug discontinuation.

Small- or medium-vessel vasculitides, thrombotic thrombocytopenic purpura, and viral arthritis, as seen in parvovirus infection and HIV/AIDS, can also mimic SLE. Differential diagnosis relies on laboratory studies, detection of viral serologies, and tissue histopathology. Hematopoietic cancer and malignant lymphoproliferative syndromes may present with positive ANA, anemia, low-grade fever, pleural effusions, and lymphadenopathy and can be misdiagnosed as lupus.

When should clinicians consider consulting with a rheumatologist or other specialist for diagnosing patients with possible lupus?

Clinicians should consult a rheumatologist in all patients when clinical manifestations and serologic studies suggest SLE. Evidence of renal, pulmonary, CNS, ocular, or gastrointestinal disease necessitates a coordinated, multidisciplinary 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 as a diagnostic challenge because it can include cutaneous, renal, respiratory, cardiovascular, CNS, and gastrointestinal manifestations that characterize numerous 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, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 2). Hydroxychloroquine prevents disease flares

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Table 2. Drug Treatment for SLE

Agent	*Mechanism of Action*	*Dosage*	*Common Side Effects*
NSAIDs	Anti-inflammatory		Gastritis, nephrotoxicity, fluid retention
Glucocorticoids	Anti-inflammatory effect due to negative transcriptional regulation of pro-inflammatory genes	Low: ≤7 mg/d; medium: >7–≤30 mg/d; high: >30–≤ 100 mg/d; very high: >100 mg/d; pulse: 250 mg/d (27)	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-TG and 6-MMP 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 (IV 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 pro-inflammatory cytokines	2.5–4.5 mg/kg/d (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 IV at 2-wk intervals and then 10 mg/kg IV every mo	Hypersensitivity reaction, gastrointestinal toxicity, myalgias, depression, migraine, infection
Rituximab	Depletes CD20-expressing B-lymphocytes	Two 1000 mg doses given IV at 2-wk intervals; may be repeated every 6 mo	Infusion reaction, infection, progressive multifocal leukoencephalopathy (rare)

and is considered 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.

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

Hydroxychloroquine and other antimalarial agents have been used to treat inflammatory arthritides for at least 50 years (20). In addition to preventing lupus relapses and reducing the risk for congenital

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heart block in neonatal SLE, hydroxychloroquine has antithrombotic effects that are particularly important to SLE patients with antiphospholipid antibody-related prothrombotic diathesis (21). Hydroxychloroquine is generally well-tolerated, and the rare risk for retinopathy is directly related to the years of exposure to the drug and the age of the patient.

In a study of 29 cases of antimalarial retinal toxicity over a period of 30 years, all patients were older than 40 years and had had exposure to the agents over 5 years (22).

Skin hyperpigmentation 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, should be treated with glucocorticoids administered intravenously (IV) in conjunction with immunosuppressive medications. Glucocorticoids can be gradually withdrawn once remission is achieved. Oral prednisone or methylprednisolone is used for arthritis, pleuropericarditis, cutaneous vasculitis, and uveitis.

Early studies demonstrated that glucocorticoids could ameliorate SLE, although subsequent controlled trials showed that the therapeutic effect was not sustained (23). Early studies also linked glucocorticoids to improved survival in severe SLE (24), but similar studies have not been done for mild or moderate disease. Current decisions about glucocorticoid dosage and the duration of treatment for specific manifestations rely largely on clinical experience because too few clinical trials have been done.

An early study comparing 100 mg with 1000 mg of IV methylprednisolone suggested that 3 daily doses of 1000 mg did not have a significant advantage over 3 daily doses of 100 mg (25). A more recent randomized study showed that a dose of 1000 mg to 1500 mg over 3 days is as effective as doses ranging from 2000 mg to 5000 mg over 3 days and is associated with a decreased risk for infections (26).

Significant overlap exists between lupus manifestations and some glucocorticoid complications, including osteoporosis, avascular bone necrosis, myopathy, and psychosis. Furthermore, despite the abundance of observational data on glucocorticoid toxicity, evidence from randomized, controlled clinical trials (RCTs) is limited. Table 2 summarizes the 2002 European League Against Rheumatism recommendations on glucocorticoid treatment (27). These recommendations define a low daily dose of prednisone (or equivalent) as ≤7 mg. Low doses are associated with relatively low risk for toxicity, although monitoring for cushingoid symptoms, osteoporosis, cataracts, glaucoma, hyperglycemia, and hypertension is probably justified. Prolonged treatment with medium to high doses carries a higher risk for complications, including myopathy, psychosis, hyperlipidemia, and atherosclerosis. However, the prevalence and incidence of these complications in different corticosteroid regimens are still unclear (28).

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. Their efficacy has been shown by RCTs. Such trials have also shown 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 on

case reports or prospective, nonrandomized studies (9).

How should clinicians choose drug therapy for lupus arthritis?

Low-dose glucocorticoids and antimalarials are first-line agents for treating arthritis in lupus. Methotrexate is often used for arthritis or cutaneous disease, particularly in patients without other systemic manifestations.

A double-blind RCT showed that methotrexate is effective in controlling cutaneous and articular symptoms in SLE (29). These findings were also supported by a recent open-label trial (30) and an RCT showing that methotrexate can be used as a steroid-sparing agent in SLE (31).

Methotrexate antagonizes folic acid and inhibits purine and pyrimidine synthesis. In addition, it 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?

Induction therapy

The indications for kidney biopsy are in the Box: Indications for Kidney Biopsy in Patients With SLE; the currently accepted classification system for biopsy results are in the Box: Histopathologic Classification of Lupus Nephritis.

Class I or II lupus nephritis does not require immunosuppressive therapy. Class III or IV is treated aggressively. Until recently, cyclophosphamide combined with intravenous glucocorticoids has been the standard of care for induction therapy of class III and IV lupus nephritis. Cyclophosphamide is an alkylating agent that promotes DNA cross-linking and affects T- 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. Current ACR recommendations are based on expert opinion and consensus.

Early open-label trials and RCTs showed short-term efficacy of glucocorticoids for treatment of lupus nephritis. Subsequently, an RCT comparing cyclophosphamide to glucocorticoids showed superiority of cyclophosphamide for induction therapy of proliferative lupus nephritis. Nonresponse was more common in the group treated with IV glucocorticoids and the probability of achieving remission was higher in the glucocorticoid plus cyclophosphamide group (32).

Long-term follow-up of the study participants indicated that an increase in creatinine by 50% or 100% was less common in patients receiving combination treatment (33).

Over the past decade, several studies have shown efficacy of mycophenolate mofetil for induction therapy in lupus nephritis (34–36). This drug is metabolized to mycophenolic acid, an inhibitor of inosine 5-monophosphate dehydrogenase, which is required for de novo synthesis of guanosine nucleotides. Mycophenolate mofetil 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 (37).

In a meta-analysis of 4 selected RCTs evaluating the efficacy of mycophenolate mofetil vs. cyclophosphamide for induction therapy, when data on maintenance therapy were excluded mycophenolate mofetil

Indications for Kidney Biopsy in Patients With SLE*

- Increasing serum creatinine without compelling alternative causes
- Confirmed proteinuria ≥1.0 g/24 h (either 24-h urine specimens or spot protein–creatinine ratio)
- Combination of the following: Proteinuria ≥0.5 ≥1.0 g/24 h + hematuria (≥5 red blood cells/high-power field) or proteinuria ≥0.5 ≥1.0 g/24 h + cellular casts

* From reference 38.

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

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. 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]
48. Spetie DN, Tang Y, Rovin BH, et al. Mycophenolate therapy of SLE membranous nephropathy. Kidney Int. 2004;66:2411-5. [PMID: 15569333]

was not superior to cyclophosphamide in lupus nephritis (36).

Recently updated guidelines recommend using either cyclophosphamide or mycophenolate mofetil combined with glucocorticoids for induction therapy of class III or IV proliferative lupus nephritis (38). Response to cyclophosphamide or mycophenolate mofetil may differ based on race. Asians and Europeans seem to respond better to cyclophosphamide than Hispanics and African Americans (38).

Maintenance therapy

Current guidelines recommend either mycophenolate mofetil or azathioprine for maintenance therapy in lupus nephritis. Both are superior to cyclophosphamide for this purpose (39). Evidence from 2 studies of comparative efficacy of mycophenolate mofetil vs. azathioprine is conflicting (40, 41). Treatment duration is guided by clinical experience.

In a study of 227 patients with lupus nephritis class III, IV, or V who showed a clinical response to a 24-week induction with either cyclophosphamide or mycophenolate mofetil, patients were randomly assigned to treatment with mycophenolate mofetil (2 g/d) or azathioprine (2 mg/kg/d). After 3 years of follow up, mycophenolate mofetil was significantly superior to azathioprine with respect to time to treatment failure (primary end point), time to renal flare, and time to rescue therapy (40).

In contrast, an open-label study showed no significant difference in patients treated with mycophenolate mofetil vs. azathioprine for maintenance treatment of lupus nephritis over a period of 4 years. All patients in the study were initially treated with low-dose cyclophosphamide for induction therapy (41).

Calcineurin inhibitors, such as cyclosporine, are also used for maintenance therapy.

A multicenter, randomized, open pilot trial compared the efficacy of cyclosporine vs. azathioprine for maintenance therapy of lupus nephritis. Seventy-five patients with lupus nephritis IV, Vc, or Vd, initially treated with IV glucocorticoids (1 mg/kg/3 d) followed by oral cyclophosphamide and prednisone for a median of 90 days, were randomized to treatment with azathioprine or cyclosporine for 2 (core study) and 4 years. Azathioprine and cyclosporine were equally effective in preventing disease flares, the primary outcome of the study. Proteinuria, a secondary end point, decreased significantly with both treatments. Blood pressure and creatinine clearance did not change significantly with either treatment; extrarenal manifestations and clinical activity decreased with both treatments (42).

Data from this study indicate that cyclosporine and azathioprine are equally effective for maintenance treatment of lupus nephritis and have similar effects on blood pressure and renal function.

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 (43).

Rituximab is a monoclonal antibody directed against CD20, a membrane protein expressed on B-cells. Rituximab depletes B-cells from the peripheral blood. Open-label trials indicated improvement of lupus nephritis after B-cell depletion; however, RCTs did not show statistically significant response compared with placebo (44–46).

Current ACR guidelines propose mycophenolate mofetil or azathioprine as preferred maintenance therapy for proliferative lupus nephritis. Calcineurin inhibitors or rituximab combined with glucocorticoids may be used for patients with an adequate response to cyclophosphamide or mycophenolate mofetil (38). To date, no RCT has directly compared calcineurin inhibitors to mycophenolate mofetil for maintenance treatment of class III or IV lupus nephritis.

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.

A retrospective analysis of 2 large RCTs showed similar efficacy of mycophenolate mofetil and cyclophosphamide for induction therapy of class V lupus nephritis (47).

A prospective study of mycophenolate mofetil combined with renoprotective therapy (with angiotensin inhibitors or angiotensin-receptor blockers) showed that most patients achieved complete or partial remission at 6 months and sustained effect for a mean follow-up of 18 months (48).

Based on this evidence, current guidelines from the ACR for membranous lupus nephritis recommend treatment with mycophenolate mofetil. Tacrolimus and azathioprine have also been studied for induction or maintenance treatment.

A recent open-label trial showed that tacrolimus or mycophenolate mofetil combined with steroids were both effective in controlling membranous lupus nephritis (49).

An RCT comparing azathioprine with tacrolimus, both combined with prednisone, for maintenance therapy of membranous nephritis suggests similar low rates in relapse with both regimens (50).

How should clinicians choose therapy for neuropsychiatric lupus?

Treatment of serious neuropsychiatric SLE manifestations is relatively empirical and includes IV glucocorticoids, immunoglobulin, and cyclophosphamide.

An RCT comparing cyclophosphamide with glucocorticoids after 3 days of IV immunoglobulin for treatment of transverse

myelitis in lupus showed that relapse was more common in the steroid group (51).

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.

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 IV glucocorticoids and immunosupressants. 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 (52). SLE patients with pulmonary hypertension are at high risk for cardiac failure and early death. Endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs with or without immunosuppressive medications may be used to treat pulmonary hypertension in lupus.

An RCT showed efficacy of cyclophosphamide in mild and moderate pulmonary hypertension in patients with SLE by reducing pulmonary artery systolic pressure and improving the New York Heart Association functional class (53).

A retrospective study suggests that patients with SLE and mild to moderate pulmonary hypertension may respond to treatment with cyclophosphamide and glucocorticoids, while patients with more severe disease may require combination of vasodilators with immunosuppressants (54).

A small study indicated that interstitial lung disease treated with glucocorticoids for at least 1 week resulted in indolent progression or stabilization over time (55).

Larger clinical trials have not been done, and treatment decisions are based on clinical experience.

Azathioprine or cyclophosphamide is frequently recommended for patients who have not responded to glucocorticoids (56). 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 antimalarial agents, NSAIDs, or oral or IV glucocorticoids. Scleral or retinal involvement may require concomitant use of pulse glucocorticoids, followed by 1 mg/kg of prednisone equivalent, combined with immunosuppressive therapy (57). 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.

What new medications are available for treating systemic lupus?

A monoclonal antibody targeting the B-lymphocyte stimulator (BLys) was recently approved.

Two international, double-blind, phase 3 RCTs compared belimumab 1 mg/kg and 10 mg/kg plus standard therapy to placebo plus standard therapy (58, 59). In the 52-week study, reduction of ≥4 points on the SLE Response Index (SRI) was 51% and 58% with the belimumab 1-mg/kg and 10-mg/kg dose, respectively, vs. 44% with placebo ($P<0.05$). In the 76-week study, the SRI-measured response at 52 weeks was 42.8% and 46.5% with the belimumab 1-mg/kg and 10-mg/kg dose and 35.3% with placebo; at 76 weeks, the response rates were 42.1% and 41.4% with the belimumab 1-mg/kg and 10-mg/kg dose, and 33.8% with placebo ($P<0.05$ and $P = NS$, respectively). Both trials excluded patients with severe lupus nephritis or severe CNS manifestations. Analysis of combined results from both trials showed more improvement of musculoskeletal and mucocutaneous manifestations in patients treated with belimumab and improvement

49. Yap DY, Yu X, Chen XM, et al. Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome. Nephrology (Carlton). 2012;17:352-7. [PMID: 22295934]
50. Chen W, Liu Q, Chen W, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. Lupus. 2012;21:944-52. [PMID: 22438027]
51. Kovacs B, Lafferty TL, Brent LH, et al. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann Rheum Dis. 2000;59:120-4. [PMID: 10666167]
52. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. Clin Dev Immunol. 2012;2012:854941. [PMID: 22489252]
53. Gonzalez-Lopez L, Cardona-Muñoz EG, Celis A, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. Lupus. 2004;13:105-12. [PMID: 14995003]
54. 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]
55. Weinrib L, Sharma OP, Quismorio FP Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. Semin Arthritis Rheum. 1990;20:48-56. [PMID: 2218553]

56. Pego-Reigosa JM, Medeiros DA, Isenberg DA. Respiratory manifestations of systemic lupus erythematosus: old and new concepts. Best Pract Res Clin Rheumatol. 2009;23:469-80. [PMID: 19591778]
57. Neumann R, Foster CS. Corticosteroid-sparing strategies in the treatment of retinal vasculitis in systemic lupus erythematosus. Retina. 1995;15:201-12. [PMID: 7569347]
58. Furie R, Petri M, Zamani O, et al; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918-30. [PMID: 22127708]
59. Navarra SV, Guzmán RM, Gallacher AE, et al; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:721-31. [PMID: 21296403]
60. 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]
61. 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]
62. Mok CC, Ho LY, Fong LS, To CH. 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]

in immunologic parameters; in addition, fewer patients had worsening hematologic parameters (60).

The SRI requires reduction in disease activity scores and no deterioration from baseline in target organ manifestations (58). Further evidence is needed to assess the comparative efficacy of BlyS antagonism in severe lupus manifestations.

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 double-stranded DNA antibodies and complement C3 and C4 levels; however, this practice is controversial for clinically stable patients. Although a prospective RCT showed that 4-week treatment with prednisone of clinically stable but serologically active patients averts a severe flare (61), C3 and C4 and double-stranded DNA antibodies are more useful in assessing SLE activity in symptomatic patients or in assessing response to treatment. Other monitoring should be tailored to individual disease manifestations (Table 3). Consideration should be given to laboratory monitoring for immunosuppressive medication toxicity and ophthalmologic evaluation of patients treated with hydroxychloroquine, particularly those older than 40 years who have been treated for a long period. Clinicians should be alert to osteoporosis prevention and prescribe treatment when appropriate. Clinicians should also consider periodic lipid testing and order lipid-lowering agents, as needed.

What should clinicians do about immunizations in people with lupus?

All patients with SLE should receive influenza and pneumococcal vaccinations. In addition, a recent study showed that the quadrivalent human papillomavirus vaccine is well-tolerated and reasonably effective in patients with stable SLE and does not induce an increase in lupus activity or flares (62). Patients receiving immunosuppressive therapy or daily prednisone >20 mg should not receive live attenuated vaccines, including herpes zoster (shingles), Flumist, measles-mumps-rubella, and smallpox. Tuberculin skin testing is recommended for SLE patients requiring prolonged treatment with glucocorticoids or immunosuppressive therapy.

How should clinicians modify treatment for pregnant patients?

Fertility is not significantly affected in SLE; however, flares occur at a higher rate during pregnancy and the immediate postpartum period. The presence of anti-SSA antibodies may predict adverse pregnancy outcomes, as may other factors, including antiphopsholipid antibodies, renal disease, thrombocytopenia, hypertension, and use of prednisone. Becoming pregnant during clinical remission correlates with less frequent and severe lupus exacerbations. The initial presentation of SLE with hematologic or renal manifestations during pregnancy is not uncommon. Clinicians should also consider pregnancy-related hematologic, vascular, and renal abnormalities that mimic SLE manifestations, including eclampsia and the HELLP syndrome (a group of symptoms that occurs in pregnant women with hemolysis, elevated liver enzymes, and low platelet counts). Antimalarials can be used safely in pregnant SLE patients (63). Active lupus manifestations in

pregnancy are usually treated with hydroxychloroquine and prednisone. It is advisable to continue hydroxychloroquine in pregnancy because discontinuation is associated with increased risk for flares and pregnancy is associated with risk for increased disease activity. Hydroxychloroquine may also protect against cardiac manifestations of neonatal lupus.

For severe manifestions, IV glucocorticoids and azathioprine may be considered because azathioprine has not been identified as a human teratogen (64). Mycophenolate mofetil, cyclophosphamide, and methotrexate are contraindicated due to potential teratogenicity.

When should patients with lupus 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. SLE patients with unexplained fever should be hospitalized for evaluation and initiation of treatment with antibiotics. Empirical coverage should include *Staphyloccocus aureus*, *Pseudomonas* species, *Klebsiella* species, *Escherichia coli,* and *Acinetobacter* species. Chest pain in lupus patients could be due to coronary artery disease, serositis, pulmonary embolism, or esophageal disease. Lupus increases the risk for endothelial dysfunction, and long-term treatment with steroids increases traditional risk factors for coronary artery disease (65). Neurologic symptoms in lupus patients may be due to neuropsychiatric lupus, infection, the antiphospholipid syndrome, or hypertension. All lupus patients with acute neurologic manifestations should be admitted and rapidly evaluated with appropriate imaging, cerebrovascular fluid analysis, echocardiogram, and laboratory studies.

Table 3. Recommended Follow-up of Patients With SLE

Issue	*How*	*Frequency*
Disease activity	History (rash, joint pain constitutional symptoms); physical examination; CBC, urinalysis, CMP	Quarterly
Nephropathy	CMP, urinalysis, urine protein–creatinine ratio	Quarterly, if inactive disease, or monthly, to assess response to treatment
Hyperlipidemia	Fasting lipid profile	Yearly
Hydroxychloroquine toxicity	History (visual disturbances); ophthalmologic evaluation	Yearly
MMF, AZA toxicity	CBC, CMP	Every 8–12 wk or 4 wk after change in dose
Cervical dysplasia on immunosuppressants	Gynecologic examination; PAP smear, HPV test	Yearly
Osteonecrosis	History, x-rays or MRI of affected joint	With symptoms and history suggestive of avascular necrosis
Thrombosis	History, examination venous duplex studies, imaging for pulmonary embolism	With symptoms or signs suggestive of thrombosis
Pulmonary hypertension	Echocardiography	Yearly, or as clinically indicated
Osteoporosis	DEXA	Every 1–2 years, while on steroids
Planned pregnancy	Antiphospholipid antibodies urinalysis, anti-SSA/SSB antibodies, CBC, CMP, and complement C3 and C4	Before conception
Patient education		Every visit

AZA = azathioprine; CBC = complete blood count; CMP = comprehensive metabolic panel; DEXA = dual x-ray absorptiometry; HPV= human papillomavirus; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; PAP = Papanicolaou.

When should clinicians consider consulting a rheumatologist or other specialist?

A rheumatologist should be involved in the treatment of all lupus patients (66). Other specialists also may be involved, according to organ-specific disease manifestations.

What nondrug therapies should clinicians recommend?

All lupus patients should be counseled on low-cholesterol diet,

63. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum. 2003;48:3207-11. [PMID: 14613284]
64. Natekar A, Pupco A, Bozzo P, Koren G. Safety of azathioprine use during pregnancy. Can Fam Physician. 2011;57:1401-2. [PMID: 22170192]

exercise, weight control, and smoking cessation. They should also be advised about protection from ultraviolet rays to reduce flares from sun exposure. Prevention or treatment of complications due to conditions commonly associated with lupus, such as osteoporosis or the Sjogren syndrome, is also recommended. All patients should be counseled on the daily requirements for calcium and vitamin D to prevent osteoporosis. Routine dental evaluation is also recommended.

65. Petri M, Lakatta C, Magder L, et al. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. Am J Med. 1994;96:254-9. [PMID: 8154514]

66. Gabriel S, Tugwell P, O'Brien B, et al. Report of the OMERACT task force on economic evaluation. Outcome Measures in Rheumatology. J Rheumatol. 1999;26:203-6. [PMID: 9918264]

Treatment... Hydroxychloroquine prevents disease flares and is considered 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 classification and guided by ACR recommendations. 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

In the Clinic
Tool Kit

Systemic Lupus Erythematosus

PIER Module

http://smartmedicine.acponline.org/content.aspx?gbosId=153
Smart Medicine module on systemic lupus erythematosus (SLE) from the American College of Physicians.

Patient Information

www.nlm.nih.gov/medlineplus/lupus.html
www.nlm.nih.gov/medlineplus/tutorials/lupus/htm/index.htm
www.nlm.nih.gov/medlineplus/spanish/tutorials/lupusspanish/htm/index.htm
Resources related to lupus from the National Institutes of Health's MedlinePLUS, including an interactive tutorial in English and Spanish.

www.niams.nih.gov/Health_Info/Lupus/lupus_ff.asp
www.niams.nih.gov/Portal_En_Espanol/Informacion_de_Salud/Lupus/default.asp
Answers to common questions about lupus from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), in English and Spanish.

www.nlm.nih.gov/medlineplus/ency/article/000481.htm
Information about lupus nephritis, a complication of SLE from NIAMS.

Clinical Guidelines

www.rheumatology.org/Practice/Clinical/Guidelines/Glucocorticoid-Induced_Osteoporosis_(Members__Only)/
Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis from the American College of Rheumatology (ACR) in 2010.

Diagnostic Tests and Criteria

pier.acponline.org/physicians/diseases/d208/tables/d208-tlab.html
List of laboratory and other studies for SLE from PIER.

www.rheumatology.org/practice/clinical/position/ana_position_stmt.pdf
Position statement on the methodology of testing for antinuclear antibodies from the ACR in 2011.

In the Clinic