Psoriatic Arthritis

Table 18 lists agents available to treat psoriatic arthritis. In general, most of these agents are also effective for psoriasis. Because agents such as TNF inhibitors are often given in higher doses for skin disease than for joint disease, the predominant feature of the disease may drive the prescribing dose. Weight loss and smoking cessation may positively affect disease activity.

For limited disease, such as a single digit with dactylitis or a single swollen joint, an oral or topical NSAID or a local injection of glucocorticoids may suffice. High-dose oral glucocorticoids should be avoided because eventual tapering of the dosage raises the risk for erythrodermic psoriasis.

For more active disease, the ACR suggests initiating a TNF inhibitor, methotrexate, or an interleukin-17 inhibitor. If one agent is insufficient, another may be tried. Combination therapy does not have the same effect in psoriatic arthritis as in rheumatoid arthritis. Surgery may be indicated for significant damage to larger joints.

Enteropathic Arthritis

Enteropathic arthritis is best addressed by focusing on control of bowel inflammation. For spondyloarthritis associated with bowel involvement, medications to address both peripheral arthritis and bowel inflammation include sulfasalazine, azathioprine, methotrexate, and glucocorticoids. The TNF inhibitors are especially useful for bowel and joint symptoms, including spine disease. Interleukin-17 inhibitors may cause IBD to flare and are contraindicated in these patients. NSAIDs should be avoided when possible because of the potential for IBD flare.

Reactive Arthritis

Because of a lack of benefit, antibiotic treatment of reactive arthritis due to enteric organisms is not usually warranted. However, patients with severe infections or immunosuppression or those with urogenital infection with *C. trachomatis* may benefit from antibacterial therapy.

TABLE 18. Medications to Treat Psoriatic Arthritis

Category	Medications
Anti-inflammatory agents	NSAIDs; oral or intra-articular glucocorticoids
Nonbiologic disease-modifying antirheumatic drugs	Methotrexate, leflunomide, sulfasalazine, cyclosporine, apremilast
Tumor necrosis factor inhibitors	Etanercept, adalimumab, infliximab, certolizumab, golimumab
Interleukin-17 inhibitors	Secukinumab, ixekizumab, brodalumab
Interleukin-12/interleukin-23 inhibitor	Ustekinumab
Cytotoxic T-lymphocyte antigen-4 immunoglobulin	Abatacept
Janus kinase inhibitor	Tofacitinib

For mild arthritic disease, NSAIDs or joint injections with glucocorticoids may be sufficient until the disease self-resolves. For more persistent or severe disease, sulfasalazine (preferred) or methotrexate may be required. There are few data from controlled studies for either agent, but case series and reports suggest efficacy. TNF inhibitors may also be needed if these agents fail, but again data are scant. Given the monophasic nature of reactive arthritis in many patients, a trial off therapy is warranted 3 to 6 months after remission.

Topical glucocorticoids can be used to help address the skin manifestations, and topical ocular glucocorticoids are useful for uveitis.

KEY POINTS

- For ankylosing spondylitis, NSAIDs are recommended as the initial medication to relieve pain and improve stiffness; physical therapy to maintain general range of motion is essential.
- Tumor necrosis factor inhibitors in patients with active ankylosing spondylitis are associated with improvements in clinical, radiographic, and MRI outcomes.
- For psoriatic arthritis, limited disease can be treated with a topical NSAID or local glucocorticoid injection; for more active disease, a tumor necrosis factor inhibitor, methotrexate, or interleukin-17 inhibitor can be used.
- The peripheral arthritis tied to inflammatory bowel disease is best addressed by focusing on control of bowel inflammation; for spondyloarthritis that is associated with bowel involvement, medications to address both peripheral arthritis and bowel inflammation include sulfasalazine, azathioprine, methotrexate, and glucocorticoids.
- Because of a lack of benefit, antibiotic treatment of reactive arthritis due to enteric organisms is not usually warranted; for mild arthritic disease, NSAIDs or joint injections with glucocorticoids may be sufficient, and for more persistent or severe disease, sulfasalazine or methotrexate may be required.

Systemic Lupus Erythematosus

Epidemiology and Pathophysiology

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by a heterogeneous constellation of organ involvement and the presence of antinuclear antibodies (ANA) and other autoantibodies.

In SLE, a complex and varying interaction of genes, environment, and random events leads to a breakdown of self-tolerance and autoimmunity. Defects in cellular apoptosis

result in inadequate clearance of intracellular proteins, especially nuclear antigens, promoting the generation of self-directed T and B cells and the initiation/propagation of autoimmunity. Cytokine generation supports autoreactivity, with type 1 interferons playing a major role. Autoantibodies may directly induce tissue damage or promote the formation of immune complexes that lead to complement activation and tissue inflammation and damage. Inheritance of SLE risk is polygenic, including major histocompatibility complex genes.

The risk for SLE is higher in those with a family history. Incidence increases at puberty and peaks in the third decade. The disease is more common and more severe in Black and Hispanic populations. Approximately 90% of adult patients are women; SLE is frequently more severe in men than women.

KEY POINTS

- Systemic lupus erythematosus is a multisystem autoimmune disease characterized by a heterogeneous constellation of organ involvement and the presence of antinuclear antibodies and other autoantibodies.
- Approximately 90% of adult patients with systemic lupus erythematosus are women.

Clinical Manifestations

Mucocutaneous Involvement

Skin disease occurs in most patients with SLE and is classified as acute, subacute, or chronic.

Acute cutaneous lupus erythematosus (ACLE) presents as an erythematous, macular, patchy eruption, sometimes with desquamation. The facial eruption of ACLE (the classic malar or butterfly rash) is characterized by fixed, rather than transient, erythema/edema over the cheeks and bridge of the nose, sparing the nasolabial folds (**Figure 29**), but the neck, upper chest, and dorsum of the arms and hands can also be involved. In some patients, a bullous eruption occurs. ACLE usually responds to therapy and heals without scarring or atrophy.

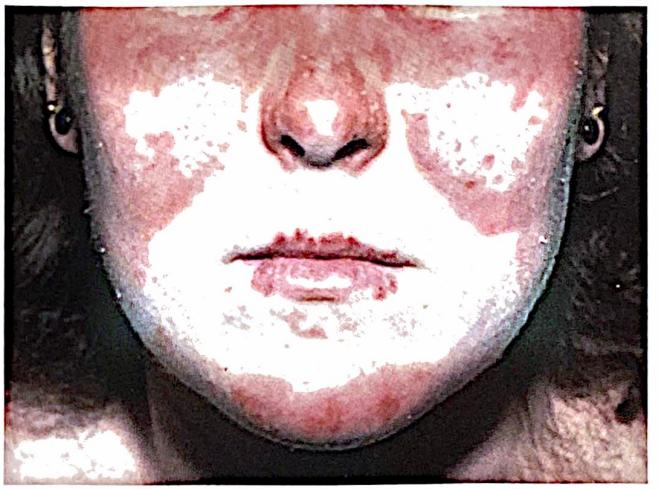

FIGURE 29. The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash). This patient has fixed erythematous raised lesions over the malar eminences, the bridge of the nose with sparing of the nasolabial folds, and the chin.

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive rash occurring especially on the arms, neck, and upper trunk, usually sparing the central face (**Figure 30**). It consists of erythematous annular/polycyclic or patchy papulosquamous lesions, often with a fine scale, that may leave

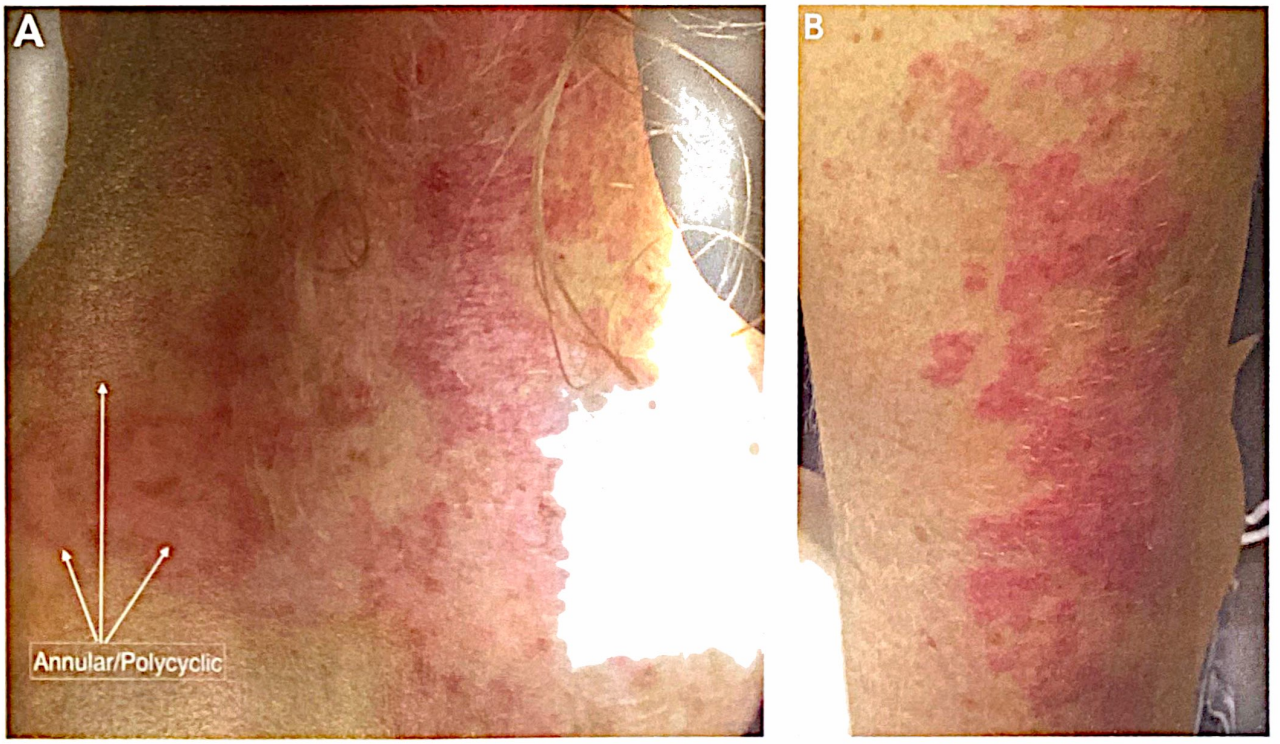

FIGURE 30. Subacute cutaneous lupus erythematosus is characterized by erythematous, macular, or patchy skin lesions that are scaly and can evolve as (*A*) annular/polycyclic lesions or (*B*) papulosquamous plaques.

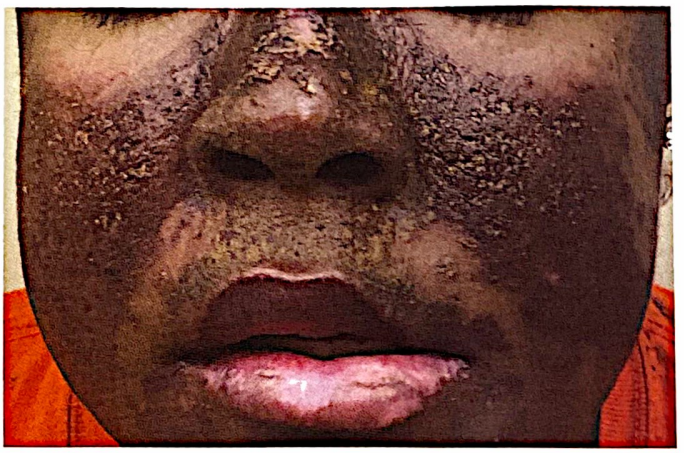

FIGURE 31. Discoid lupus erythematosus. This patient has hyperpigmented, raised patches with keratotic scaling and follicular plugging involving the malar and perioral areas as well as the bridge of the nose. Areas of atrophic scarring are also present.

postinflammatory hypo- or hyperpigmentation. SCLE is associated with anti-Ro/SSA autoantibodies (prevalence >75%) and can occur in isolation or as a manifestation of underlying SLE.

Discoid lupus erythematosus (DLE) is the most common manifestation of chronic cutaneous lupus erythematosus and can cause scarring, atrophy, and permanent alopecia (**Figure 31** and **Figure 32**). DLE presents as hypo- or hyperpigmented patches or plaques, with erythema during active disease, which may be variably atrophic or hyperkeratotic. Like SCLE, DLE can occur as an isolated finding in the absence of SLE and in such cases is typically limited to the neck, face, and scalp.

Painless oral or nasopharyngeal ulcerations occur in 5% of patients with SLE. Involvement of the hard palate is characteristic. Rarely, DLE is associated with painful ulcers. Nonscarring alopecia is a common feature of active SLE, with hair regrowth a sign of disease control.

Raynaud phenomenon occurs frequently, reflecting arterial vasospasm of digital arteries. Other vascular changes, including livedo reticularis or periungual erythema, may be present as well, although these findings are nonspecific. Some patients with SLE may develop cutaneous vasculitis, most often in the distal extremities.

Musculoskeletal Involvement

Joints are affected in 90% of patients with SLE. Many patients have arthralgia, and a much smaller group exhibits arthritis. Many patients with SLE may have evidence of synovitis on imaging even with minimal symptoms or swelling on examination. Typical distribution includes small peripheral joints, often resembling rheumatoid arthritis, but large joints are also affected. SLE arthritis is nonerosive, but reducible subluxation of the digits, swan neck deformities, and ulnar deviation (Jaccoud arthropathy) can occur, a result of damage to the tendons and ligaments.

Osteonecrosis is a serious complication of SLE that most commonly affects the hips but can also involve other large joints. It should be suspected in patients with otherwise unexplained pain and/or reduced range of motion. Long-term and higher-dose (>20 mg/d) prednisone treatment, severe/active SLE, and vasculitis are associated with increased risk for osteonecrosis. MRI may be needed to identify early disease. Although small lesions can improve without invasive treatment, larger areas of involvement can lead to bony collapse. Treatment requires extended non–weight-bearing and, in some cases, core decompression of the affected bone. In the wake of collapse, joint replacement may be necessary.

Myalgia and subjective weakness are common, but true myositis is rare. Glucocorticoids often cause muscle weakness, and, rarely, antimalarial agents can affect muscle. Thus, medication effects must be differentiated from active SLE disease. Fibromyalgia is a common comorbidity (30%); symptoms may overlap those of active SLE disease.

Kidney Involvement

Kidney disease occurs frequently among patients with SLE and remains an important source of morbidity. Lupus nephritis can present with minimal laboratory abnormalities (non-nephrotic proteinuria, hematuria), nephritis (hypertension, edema, active urine sediment, and elevated serum creatinine), and/or nephrosis (nephrotic-range proteinuria, edema, hypoalbuminemia, hypercholesterolemia, and, in some cases, thrombosis). Untreated active disease may progress to kidney failure, in severe cases requiring dialysis or transplant.

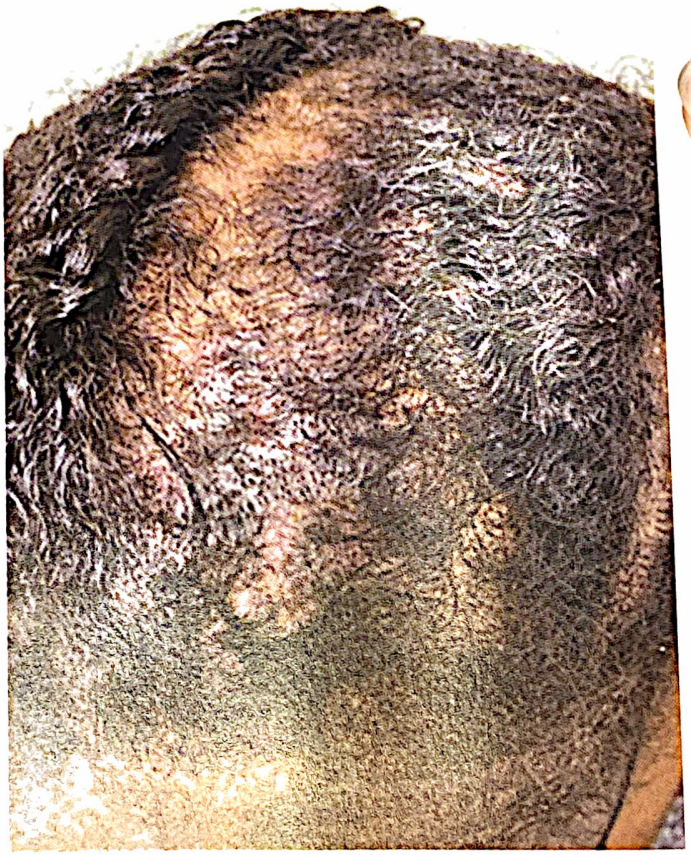

FIGURE 32. Active discoid lupus erythematosus of the scalp with scarring hair loss.

All patients with SLE should be regularly evaluated for kidney involvement through assessment of serum creatinine and urine for protein and microscopic evaluation. Active kidney disease should be suspected when there is active urine sediment or proteinuria greater than 500 mg/24 h (or a spot urine protein-to-creatine ratio >500 mg/g). Elevated or rising anti–double-stranded DNA antibody titers or complement consumption are commonly associated with active kidney disease.

Kidney biopsy defines both the histologic subtype and the activity/chronicity of disease, which are important for therapeutic decisions. Indications for kidney biopsy include an increase in serum creatinine level, unexplained decrease in glomerular filtration rate, or proteinuria greater than 500 mg/24 h (or a spot urine protein-to-creatinine ratio >500 mg/g), especially in the presence of hematuria or an active urine sediment.

See MKSAP 19 Nephrology for information on the classes and treatment of lupus nephritis.

Neuropsychiatric Involvement

Neuropsychiatric systemic lupus erythematosus (NPSLE) may involve the central and/or peripheral nervous systems. NPSLE prevalence is high (75%), but most of the common manifestations (headache, mild cognitive dysfunction, and mood disorder) are nonspecific. Peripheral neuropathy occurs in 10% to 14% of patients. Severe acute presentations, including seizures and psychosis, are uncommon (<5%) but require aggressive symptomatic as well as disease-specific treatment.

Patients suspected of having serious central NPSLE, such as meningitis, stroke, and psychosis, should undergo central nervous system imaging (CT, MRI, or PET) and cerebrospinal fluid analysis as appropriate. In some patients with severe disease, measurement of cerebrospinal fluid for NPSLE-associated autoantibodies (antineuronal, anti–*N*-methyl-D-aspartate receptor, antiribosomal P, and others) may be useful. For patients suspected of having peripheral neuropathies, electromyography and nerve conduction studies should be performed. Neuropsychologic testing may help define and distinguish organic versus functional cognitive changes.

Cardiovascular Involvement

Asymptomatic pericarditis is the most frequent cardiac manifestation of acute SLE (40%). When symptomatic, features include chest pain, exudative effusion, and, rarely, tamponade or chronic constriction. Myocarditis occurs in 5% to 10% of patients with SLE and usually presents as insidious heart failure but can be acute.

Valvular abnormalities occurring in SLE include those associated with antiphospholipid syndrome (nonspecific thickening of the mitral and aortic valve leaflets, vegetations, regurgitation, and stenosis). Libman-Sacks endocarditis (noninfectious verrucous vegetations) preferentially affects the mitral valve and can cause embolic complications.

Pulmonary Involvement

Pulmonary involvement is common in SLE, with most patients presenting with pleuritis (45%-60%). Pleural effusions occur in approximately half of these patients and are typically exudative; fluid analysis may reveal lymphocytic pleocytosis and mildly depressed glucose levels.

Parenchymal lung involvement occurs in less than 10% of patients with SLE. A nonspecific interstitial pneumonia pattern is most common, and evaluation centers on assessing SLE activity and excluding other causes of diffuse parenchymal lung disease. Two rare but potentially life-threatening complications of SLE lung disease are acute lupus pneumonitis (presenting as fever, cough, dyspnea, hypoxemia, pleuritic chest pain, and infiltrates) and diffuse alveolar hemorrhage (presenting with dyspnea, hypoxemia, diffuse alveolar infiltrates, a dropping hematocrit, and a high D_{LCO}). Both carry a high mortality rate (>50%). Early recognition, rapid evaluation (CT and/or bronchoscopy with bronchoalveolar lavage or biopsy), and aggressive respiratory support combined with high-dose glucocorticoids and immunosuppression are required. With new pulmonary infiltrates, differentiation between these disorders and infection can be difficult, and antibiotics and immunosuppressive therapy are often administered simultaneously until the diagnosis is clear.

Shrinking lung syndrome is a rare but characteristic syndrome consisting of pleuritic chest pain and dyspnea, with progressive decrease in lung volumes. The cause is uncertain, but pleuropulmonary disease and/or diaphragmatic dysfunction may contribute. Immunosuppression may reverse the process in some patients.

Hematologic Involvement

In patients with SLE, normocytic, normochromic anemia of inflammation is common; autoimmune hemolytic anemia occurs in approximately 10% of cases and correlates with SLE activity. Lymphopenia/leukopenia is also common but usually mild. Thrombocytopenia occurs in 30% to 50% of cases, and approximately 10% of patients develop severe thrombocytopenia (<50,000/μL [50×10^9/L]) in isolation or in conjunction with hemolytic anemia.

Cytopenia in SLE may be caused by immune and nonimmune destructive mechanisms (including microangiopathy), medications, and kidney and liver disease. Moderate and severe or rapidly progressive cytopenia requires prompt evaluation with serologic studies and/or bone marrow biopsy. An exact cause of cytopenia may be difficult to ascertain, and a trial of medication adjustment in concert with evaluation for other causes is often necessary.

Antiphospholipid antibodies and lupus anticoagulant are present in about 40% of patients with SLE and may be associated with a false-positive result on a rapid plasma reagin test for syphilis. Most patients are asymptomatic. Thrombotic events occur in about 30% of patients; these include venous and arterial thrombosis, miscarriage, stillbirth, livedo

reticularis, and cardiac valve thickening/vegetations. The risk for thrombosis is highest in the presence of triple positivity for lupus anticoagulant, anti–β_2-glycoprotein, and anticardiolipin antibodies. Patients with SLE are at increased risk for thrombotic events even in the absence of antiphospholipid antibodies. See MKSAP 19 Hematology for more information.

Gastrointestinal Involvement

Gastrointestinal involvement is a common (40%) and underrecognized SLE manifestation. Serositis presents as abdominal pain, is usually associated with active disease, and improves with treatment. Mesenteric vasculitis, inflammation of the small and large bowel, pancreatitis, protein-losing enteropathy, and diffuse peritonitis are uncommon but may be severe and associated with cutaneous vasculitis.

Noninfectious hepatitis can occur and is associated with the presence of antiribosomal P antibodies. Patients with SLE who have Raynaud phenomenon and anti–U1-ribonucleoprotein antibodies are at increased risk for esophageal disease and reflux.

Medications used to treat SLE (NSAIDs, prednisone, mycophenolate, azathioprine) also frequently affect the gastrointestinal system and may cause esophagitis, gastritis, pancreatitis, and other manifestations.

KEY POINTS

- The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash) is characterized by erythema/edema over the chin, cheeks, and bridge of the nose, sparing the nasolabial folds.
- Many patients with systemic lupus erythematosus have arthralgia, and a much smaller group exhibits arthritis.
- All patients with systemic lupus erythematosus should be regularly evaluated for kidney involvement through assessment of serum creatinine and urine for protein and microscopic evaluation.
- The most common manifestations of neuropsychiatric systemic lupus erythematosus are headache, mild cognitive dysfunction, and mood disorder.

Comorbidities

Patients with SLE have a higher overall risk for malignancies (particularly hematologic); the risk for non-Hodgkin lymphoma is at least two to three times higher than in the general population. Malignancy risk in SLE is tied to the use of immunosuppressive agents. Higher cumulative cyclophosphamide doses are associated with increased risk for solid organ tumors, and azathioprine use is associated with an increased risk for myeloproliferative syndromes. Cervical cancer is also increased in patients with SLE, especially those receiving immunosuppressive therapies. Hydroxychloroquine use does not appear to increase malignancy risk and may be protective.

Patients with SLE have a 2- to 10-fold increased prevalence of coronary artery disease. It is the most common cause of death among older patients with SLE, even those whose lupus has become quiescent. A history of high SLE disease activity (especially nephritis) and prednisone dosages greater than 10 mg/d are independent risk factors for coronary artery disease. Patients with SLE are also at increased risk for ischemic stroke.

KEY POINTS

- Patients with systemic lupus erythematosus are at increased risk for malignancy; immunosuppressive use contributes to this increased risk.
- Patients with systemic lupus erythematosus have a 2- to 10-fold increased prevalence of coronary artery disease; high SLE disease activity and prednisone dosages greater than 10 mg/d are independent risk factors for coronary artery disease.

Diagnosis

General Considerations

The diagnosis of SLE should be considered in patients, especially young women, with any individual manifestation of SLE or with symptoms affecting multiple organ systems. The most common presenting clinical features that differentiate patients with SLE from those with other mimicking conditions include malar rash, photosensitivity, inflammatory arthritis, weight loss, and fever, along with such laboratory features as positivity for ANA, low complement levels, and presence of lupus-specific antibodies. Patients with subjective reports of fatigue, myalgia, and/or arthralgia but lacking objective findings most likely have an alternative diagnosis and should not be evaluated for SLE.

Several classification criteria for SLE have been used; although intended for recruitment of homogenous SLE populations for research studies, they can also be used to suggest a clinical diagnosis of SLE. A 2019 update of these criteria from the European League Against Rheumatism/American College of Rheumatology includes the requirement for a positive ANA result at least once, with the addition of clinical and/or immunologic criteria totaling at least 10 points on a weighted scale (**Figure 33**). These criteria compare favorably to prior published criteria, with a sensitivity of about 96% and specificity of about 93%.

Laboratory Studies

Initial evaluation for SLE includes routine laboratory testing to establish organ-specific involvement, including complete blood count, chemistry panel, and urinalysis with microscopy.

ANA should be obtained to screen for nuclear-directed autoantibodies. The most appropriate method for testing ANA is the indirect immunofluorescence assay, which is highly sensitive (>95%) for SLE but not specific. ANA tests should be interpreted in the context of the probability o

Entry Criterion

Antinuclear antibody at a titer ≥1:80 on Hep-2 cells or equivalent positive test result

↓

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 at least one occasion is sufficient. SLE classification requires at least one clinical criterion and ≥10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score.

Clinical Domains and Criteria	Weight
Constitutional	
Fever (temperature >38.3 °C)	2
Hematologic	
Leukopenia (<4000/μL [4.0 × 10^9/L])	3
Thrombocytopenia (<100,000/μL [100 × 10^9/L])	4
Autoimmune hemolysis (with positive direct antiglobulin test result)	4
Neuropsychiatric	
Delirium	2
Psychosis (delusions and hallucinations in absence of delirium)	3
Seizure (primary generalized or focal seizure)	5
Mucocutaneous (observed by clinician)	
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 (synovitis in ≥2 joints *or* tenderness of ≥2 joints with ≥30 minutes of morning stiffness)	6
Renal	
Proteinuria >0.5 g/24 h (or equivalent spot urine protein-to-creatinine ratio)	4
Renal biopsy showing class II or V lupus nephritis	8
Renal biopsy showing class III or IV lupus nephritis	10

Immunologic Domains and Criteria	Weight
Antiphospholipid antibodies	
Anticardiolipin antibodies *or* Anti-β_2-glycoprotein I antibodies *or* Lupus anticoagulant	2
Complement proteins	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody *or* Anti-Smith antibody	6

↓

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion is fulfilled.

URE 33. Classification criteria for systemic lupus erythematosus. dsDNA = double-stranded DNA; Hep-2 = human epithelial 2; SLE = systemic lupus erythematosus.

ed with permission from BMJ: Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. ;78:1151-1159. PMID: 31383717 doi:10.1136/annrheumdis-2018-214819

disease because ANA may be present in patients with other autoimmune diseases as well as in healthy individuals. Low-titer ANA (<1:80) is considered negative; even ANA at a more positive titer in the absence of specific features of SLE may be noninformative.

If the ANA result is positive and the clinical context supportive, SLE-specific autoantibodies (anti–double-stranded DNA, anti-Smith, anti–U1-ribonucleoprotein, anti-Ro/SSA, and anti-La/SSB), as well as tests for other autoimmune diseases under consideration, should be obtained to further characterize the disease (**Table 19**).

Disease activity markers, including complements C3 and C4, should be assessed initially and regularly thereafter. Complement levels are typically reduced during SLE activity, reflecting immune complex formation and complement consumption. Rising titers of anti–double-stranded DNA antibody levels may be concordant with SLE kidney disease activity. Other SLE autoantibodies, including ANA, do not reflect disease activity and need not be repeated. Erythrocyte sedimentation rate and C-reactive protein are variably associated with disease activity; some patients with SLE have little to no elevation in C-reactive protein during SLE flares, which may help distinguish flares from infection once the individual patient's pattern of responsiveness is established.

Differential Diagnosis

The differential diagnosis of SLE includes multisystem diseases, acute and chronic infections, medication effect, malignancies (particularly hematologic), and neurologic diseases (e.g., multiple sclerosis). Multisystem autoimmune diseases (ANCA-associated vasculitis, rheumatoid arthritis, adult-onset Still disease, dermatomyositis, Sjögren syndrome, and mixed connective tissue disease) have overlapping features but may be distinguished through a careful assessment of their unique manifestations.

SLE should also be distinguished from undifferentiated connective tissue disease, which presents with milder symptoms and objective abnormalities that cannot be categorized or diagnosed as a specific connective tissue disease (see Mixed Connective Tissue Disease and Undifferentiated Connective Tissue Disease).

Certain medications can cause drug-induced lupus erythematosus (DILE), which mimics SLE (**Table 20**). The syndrome is usually milder; malaise, fever, arthritis, and rash are associated with transient positivity for ANA and antihistone antibodies. Symptoms usually resolve after discontinuation of the offending agent. Kidney and central nervous system disease are uncommon. Patients with SLE are at no more risk for DILE than the general population, and medications associated with DILE are not contraindicated in patients with SLE.

KEY POINTS

- Patients with systemic lupus erythematosus typically initially present with skin and joint manifestations; many also have fever or weight loss.
- Initial evaluation for systemic lupus erythematosus includes antinuclear antibody testing as well as routine laboratory testing to establish organ-specific involvement, including complete blood count, chemistry panel, and urinalysis with microscopy.
- If results of antinuclear antibody testing are positive and the clinical context is supportive, autoantibodies specific to systemic lupus erythematosus (anti–double-stranded DNA, anti-Smith, anti–U1-ribonucleoprotein, anti-Ro/SSA, and anti-La/SSB) should be obtained to further characterize the disease.

Management

SLE most often follows a relapsing-remitting pattern (70%) with periods of inactive disease, although some patients may have a monophasic or persistently active pattern. The most commonly used instrument for monitoring disease activity is the SLE Disease Activity Index (SLEDAI), which incorporates

TABLE 19. Common Autoantibodies in Systemic Lupus Erythematosus

Autoantibody	Frequency in SLE	Comments
Antinuclear	>95%	Useful as an initial screening test; assesses multiple antigens simultaneously
Anti–double-stranded DNA	50%-60%	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Ro/SSA	30%	Associated with photosensitive rashes, discoid lupus erythematosus, and neonatal lupus erythematosus; also common when secondary Sjögren syndrome is present
Anti–U1-ribonucleoprotein	35%	Associated with Raynaud phenomenon and esophageal dysmotility; also seen in MCTD
Anti-Smith	30%	Specific for SLE; often associated with more severe disease
Anti-La/SSB	20%	Common in Sjögren syndrome; less common in SLE and neonatal lupus erythematosus
Antiribosomal P	15%	Associated with CNS lupus and lupus hepatitis

CNS = central nervous system; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus.

TABLE 20. Medications Commonly Associated With Drug-Induced Lupus Erythematosus

Medication	Antibodies Detected	Comments
Procainamide	ANA (75%); antihistone	20% develop DILE; fever; arthritis; serositis
Hydralazine	ANA (20%); antihistone	5%-8% develop DILE; fever; arthritis; rare vasculitis and kidney disease
Minocycline	ANA; ANCA; anti-dsDNA rare	Arthritis; vasculitis; autoimmune hepatitis
Antithyroid drugs	ANA; ANCA; antihistone	Vasculitic rash; rare pulmonary and kidney disease
Statins	ANA; antihistone; anti-dsDNA	SLE, SCLE, dermatomyositis, and polymyositis all reported
Calcium channel blockers	ANA; anti-Ro/SSA; antihistone rare	SCLE
Thiazide diuretics	ANA; anti-Ro/SSA; antihistone rare	SCLE
ACE inhibitors	ANA; anti-Ro/SSA; antihistone rare	SCLE
TNF inhibitors	ANA (23%-57%); chromatin and anti-dsDNA common; antihistone rare	DILE most common with infliximab, uncommon for etanercept; SLE, SCLE, DLE all reported

ANA = antinuclear antibodies; DILE = drug-induced lupus erythematosus; DLE = discoid lupus erythematosus; dsDNA = double-stranded DNA; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

both clinical and laboratory measures. Clinical remission or low disease activity are typical goals of therapy.

Pharmacologic therapy is almost always required; the choice of agents should reflect disease activity and specific organ involvement. Management requires frequent disease assessment and adjustment of treatment to reflect changing conditions (**Table 21**).

Hydroxychloroquine is a mainstay of treatment in SLE because it reduces disease-associated damage, prevents disease flares, and improves kidney and overall survival. In addition, hydroxychloroquine may reduce the risk for thrombosis, liver disease, and myocardial infarction; improve lipid profiles; and improve outcomes in high-risk pregnancies. Almost all patients with SLE without contraindications should receive hydroxychloroquine. With very rare exceptions the dosage should be limited to 5 mg/kg/d or less, and patients should receive annual monitoring by an ophthalmologist after 5 years of treatment to reduce the risk for retinal toxicity. Hydroxychloroquine can be used alone for mild disease (especially skin and joints) and in combination with other agents in severe disease.

Glucocorticoids are also used in most patients with SLE, particularly in acute disease. The glucocorticoid dose should be determined by the level of disease activity and organ systems threatened. For severe disease activity (including profound cytopenia, class III/IV nephritis, and NPSLE), high-dose glucocorticoids are recommended. For life- or organ-threatening disease (such as rapidly progressive glomerulonephritis or seizures), high-dose intravenous glucocorticoids are given, typically followed by daily oral glucocorticoids. After disease stability is achieved, glucocorticoids are tapered to the lowest effective dosage, preferably to no more than 7.5 mg/d within 4 to 6 months. Literature supports limiting exposure to glucocorticoids, especially at high doses, because of associated risk for organ damage, infection, and premature mortality. Glucocorticoids should be discontinued entirely when possible.

For moderate or severe disease, immunosuppressive therapy should be initiated concurrently with glucocorticoids to

TABLE 21. Medications Commonly Used to Treat Systemic Lupus Erythematosus

Medication	Common Uses in SLE	Important Adverse Effects
NSAIDs	Arthritis; pain; fever	Hypertension; GI bleeding; AKI
Prednisone	Used for all manifestations in varying doses	Hypertension; glucose intolerance; weight gain; infection; osteonecrosis
Hydroxychloroquine	Used in almost all patients without contraindications; especially useful for skin involvement and to prevent disease flares	GI intolerance; rash; blurry vision; retinopathy; vacuolar myopathy
Mycophenolate mofetil	Moderate to severe disease; as effective as cyclophosphamide for remission induction for nephritis	Bone marrow suppression; elevation of liver enzymes; infection
Azathioprine	Moderate to severe disease	Bone marrow suppression; elevation of liver enzymes; hematologic malignancy
Cyclophosphamide	Severe organ- or life-threatening disease	Bone marrow suppression; hemorrhagic cystitis; infection; malignancy; infertility
Belimumab	Add-on therapy for moderate to severe disease	Infusion reactions; infections

AKI = acute kidney injury; GI = gastrointestinal; SLE = systemic lupus erythematosus.

achieve and maintain disease control and to allow tapering of glucocorticoids. The choice of medication should be determined by the organs involved and disease severity. Intravenous cyclophosphamide is used as induction therapy for severe or refractory disease (e.g., severe active nephritis, acute central nervous system lupus, diffuse alveolar hemorrhage, or myocarditis), followed by maintenance therapy with mycophenolate mofetil or azathioprine. Mycophenolate mofetil is the preferred oral agent for lupus nephritis and is as effective as cyclophosphamide for induction therapy. The biologic agent belimumab is FDA approved for patients with incomplete response to conventional treatments and is useful for skin/joint involvement and moderate/severe disease. Experience suggests a possible benefit as add-on therapy for more severe organ involvement.

Less commonly used medications include quinacrine, methotrexate, leflunomide, calcineurin inhibitors, and rituximab. Other agents under investigation include proteasome inhibitors, Janus kinase inhibitors, interleukin-12 and interleukin-23 inhibitors, and other B cell–acting agents.

Adjunctive agents may be used for specific clinical features. NSAIDs can be used to treat arthritis and pleuropericarditis but are not disease modifying and may adversely affect kidney function and blood pressure. Statins and antihypertensive agents are often used to reduce cardiovascular risks. ACE inhibitors should be considered in patients with proteinuria. Adequate vitamin D intake is important in patients with SLE. Bone health should be monitored, with treatment for appropriate patients, especially those receiving glucocorticoids. Sun avoidance and regular use of sunscreen that blocks both UV-A and UV-B should be recommended for all patients with SLE.

See Principles of Therapeutics for information on SLE medication toxicities, monitoring parameters, and more. See MKSAP 19 Nephrology for details on the treatment of lupus nephritis.

KEY POINTS

HVC
- Almost all patients with systemic lupus erythematosus without contraindications should receive hydroxychloroquine because it can reduce disease-associated damage, prevent disease flares, and improve kidney and overall survival.
- Glucocorticoids are used in most patients with systemic lupus erythematosus, particularly in acute disease; after disease stability is achieved, glucocorticoids should be tapered to the lowest effective dose, ideally to discontinuation.
- For moderate or severe systemic lupus erythematosus, immunosuppressive therapy should be initiated concurrently with glucocorticoids to achieve and maintain disease control and to allow tapering of glucocorticoids.

Pregnancy and Childbirth Issues

SLE is associated with a five- to eightfold increase in miscarriage, stillbirth, premature delivery, and intrauterine growth retardation. Outcomes are worse in patients with active disease, nephritis, or anti-Ro/SSA and/or antiphospholipid antibodies. The best time to consider pregnancy is when SLE is quiescent, and conception should be planned after at least 6 months of adequate disease control.

Proteinuria may increase during pregnancy in patients with SLE, making the distinction between SLE and preeclampsia a challenge. Increases in anti–double-stranded DNA antibody titers, decreasing complement levels, or the development of active urine sediment suggests SLE as the cause. In contrast, serum urate levels are increased in preeclampsia but not during SLE flares.

Fetuses of women who have anti-Ro/SSA or anti-La/SSB antibodies are at risk for neonatal lupus erythematosus, which is characterized by rash and congenital heart block. Although the risk for congenital heart block in the offspring of an anti-Ro/SSA–positive woman is only 2%, this condition is associated with significant fetal and neonatal morbidity and mortality. After a woman bears a child with neonatal lupus erythematosus, the risk for congenital heart block is substantially increased (20%) in subsequent pregnancies. Hydroxychloroquine may reduce the overall risk. Women with SLE who have concurrent antiphospholipid syndrome are at increased risk for miscarriage.

Management of medications during SLE pregnancy is complicated. Hydroxychloroquine and low-dose glucocorticoids can be started during or continued throughout the pregnancy. Higher-dose glucocorticoids can be used to treat flare-ups or end-organ involvement. The preferred immunosuppressive agent for SLE during pregnancy is azathioprine, but this drug should be used only if necessary. Belimumab, methotrexate, mycophenolate mofetil, and cyclophosphamide should be avoided because of risks for teratogenic effects. Cyclophosphamide is associated with age- and dose-dependent infertility. See Principles of Therapeutics for information on medications and pregnancy.

KEY POINTS

- Systemic lupus erythematosus is associated with a five- to eightfold increase in miscarriage, stillbirth, premature delivery, and intrauterine growth retardation.
- The best time to consider pregnancy is when systemic lupus erythematosus is quiescent, and conception should be planned only after at least 6 months of adequate disease control.
- Fetuses of women who have anti-Ro/SSA or anti-La/SSB antibodies are at risk for neonatal lupus erythematosus (rash and congenital heart block).
- Hydroxychloroquine and low-dose glucocorticoids can be started during or continued throughout pregnancy.

Prognosis

The prognosis in SLE has improved significantly. The 5-year survival rate is 90%, although mortality remains high compared to that in age-matched controls. Early mortality is usually related to SLE disease and infections, and late mortality is related to cardiovascular disease. Factors adversely affecting survival include myocarditis, nephritis, low socioeconomic status, male sex, and age older than 50 years at diagnosis.

KEY POINT

- Factors adversely affecting survival in systemic lupus erythematosus include myocarditis, nephritis, low socioeconomic status, male sex, and age older than 50 years at diagnosis.

Sjögren Syndrome

Epidemiology and Pathophysiology

Sjögren syndrome is a systemic autoimmune exocrinopathy primarily affecting salivary and lacrimal glands. The condition is female predominant, with a female-to-male ratio between 6 and 9 to 1. Sjögren syndrome most commonly presents in the fifth and sixth decades of life, but patients of any age may be affected; a pediatric variant is also recognized. Primary Sjögren syndrome occurs in isolation; secondary Sjögren syndrome develops with other rheumatologic diseases, most commonly rheumatoid arthritis and systemic lupus erythematosus. Whereas the primary form is uncommon (ranging from 0.5 to 5 patients/1000), secondary Sjögren syndrome is often observed (10%-30%) among populations with predisposing rheumatologic conditions. Sjögren syndrome is thought to result from activation of mucosal epithelial cells by unknown stimuli. This, in turn, leads to tonic activation of the innate and adaptive immune systems, including extensive influx of lymphocytes into exocrine glands. The resulting epithelial and obliterative damage impairs the ability to produce or deliver secretions.

Clinical Manifestations

The most common presentation of Sjögren syndrome is sicca, consisting of ocular and oral dryness. Patients report gritty eyes or a foreign body sensation. Oral dryness can cause difficulty eating unmoistened food and increases the risk for dental caries. Symmetric parotid and lacrimal swelling can occur. Other exocrine glands can be involved, leading to skin and vaginal dryness. Pancreatic involvement has been reported.

Extraglandular manifestations may occur in some patients (**Table 22**). Arthralgia and fibromyalgia are common, but nonerosive arthritis in the absence of rheumatoid arthritis is uncommon. Other common extraglandular manifestations include fatigue and Raynaud phenomenon. Both peripheral and central nervous system involvement may be seen, although the former is more common. The typical peripheral nervous system manifestation is axonal polyneuropathy. Central nervous system involvement often presents as demyelinating disease, such as optic neuritis, transverse myelitis, or a multiple sclerosis–like presentation. Cutaneous, pulmonary, and kidney disease are relatively rare. Nonspecific laboratory findings include hypocomplementemia, hypergammaglobulinemia, leukopenia, and anemia of inflammation.

TABLE 22. Extraglandular Clinical Manifestations of Sjögren Syndrome

Site/Organ	Manifestation/Frequency
General	Fatigue (70%), fever (6%)
Skin	Dry skin (xerosis), cutaneous vasculitis: 10%-16%
Joint	Arthralgia/arthritis: 36%
Lung	Interstitial pneumonitis: 5%-9%
Kidney	Interstitial nephritis, type 1 (hypokalemic distal) renal tubular acidosis, glomerulonephritis: 5%-6%
Neurologic	CNS: demyelinating disease, myelopathy, cranial nerve neuropathy Peripheral nervous system: small-fiber neuropathy, mononeuritis multiplex, peripheral neuropathy 8%-27% for CNS and peripheral nervous system
Gastrointestinal	Autoimmune hepatitis, primary biliary cirrhosis: 3%-20%
Hematologic	Lymphoma, cytopenia: 2%
Other	Systemic vasculitis (7%), cryoglobulinemia (4%-12%), Raynaud phenomenon (16%), thyroid disease (10%-15%)

CNS = central nervous system.

Patients with Sjögren syndrome are at increased risk for non-Hodgkin lymphoma compared with the general population. Estimates suggest as much as a 44-fold increased risk for mucosal-associated lymphoid tissue lymphoma; this increase presumably results from an elevated risk for lymphomatous transformation due to chronic activation of tissue lymphocytes. Clinical features conferring a higher risk include lymphadenopathy, recurrent parotid gland swelling, monoclonal gammopathy, depressed C4 complement, and decreased rheumatoid factor if titer is elevated at baseline. About 5% of patients with Sjögren syndrome develop lymphoma over time, usually within the first decade after diagnosis.

Diagnosis

An evaluation for Sjögren syndrome is typically triggered when the patient reports symptoms of ocular or oral dryness. It requires objective confirmation of exocrinopathy along with