KEY POINTS (continued)

- In more severe psoriatic arthritis, tumor necrosis factor α inhibitors have been shown to have superior efficacy in the management of joint symptoms and to slow the progression of radiographic damage.
- Treatment options for both intestinal and peripheral arthritis related to Crohn disease and ulcerative colitis include sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, glucocorticoids, infliximab, and adalimumab.
- HVC Antibiotics are not usually effective in treating reactive arthritis, but short-term NSAIDs can be used to improve symptoms in this typically self-limited disease.

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 the 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.

The risk of SLE developing in genetically predisposed individuals increases at puberty and peaks in the third decade. Approximately 90% of adult patients are women. The disease is more common, and perhaps more severe, in black, Asian, and Hispanic ethnicities.

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 up to 90% 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 (malar or butterfly rash) is characterized by erythema/edema over the cheeks and bridge of the nose, sparing the nasolabial folds; it occurs in about 50% of patients with SLE (**Figure 15**). Less characteristically, ACLE can also involve the neck, upper chest, and dorsum of the arms and hands; it affects the skin between the fingers but spares the knuckle pads. In some patients, a bullous eruption can occur. ACLE usually responds to therapy and heals without scarring or atrophy.

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive rash occurring especially on the arms, neck, and face (**Figure 16**). It consists of erythematous annular/polycyclic or patchy papulosquamous lesions, often with a fine scale, that may leave 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 chronic cutaneous manifestation of SLE, occurring in 20% of patients (**Figure 17**). DLE presents as hypo- or hyperpigmented patches or plaques, with erythema during active disease, which may be variably atrophic or hyperkeratotic. Unlike ACLE and SCLE, DLE can cause scarring, atrophy, and permanent alopecia. DLE also occurs as an isolated finding in the absence of SLE. Isolated DLE is usually limited to the neck, face, and scalp, whereas discoid lesions in SLE are more diffusely distributed. Patients with isolated DLE tend to be ANA negative and usually do not progress to SLE. It is important to differentiate isolated DLE from DLE as a manifestation of

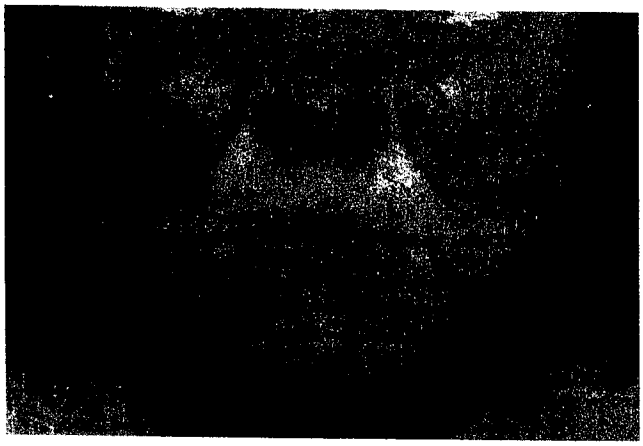

FIGURE 15. The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash). This patient has fixed erythematous raised lesions over the malar eminences, the bridge of the nose with sparing of the nasolabial folds, and the chin.

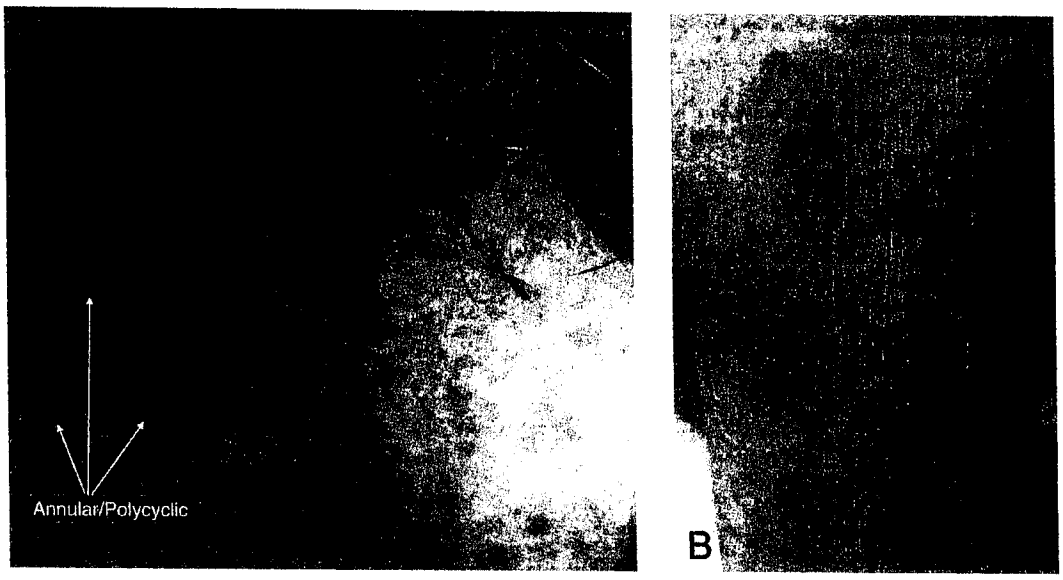

FIGURE 16. Subacute cutaneous lupus erythematosus is characterized by erythematous, macular, or patchy skin lesions that are scaly and can evolve as (*A*) annular/polycyclic lesions or (*B*) papulosquamous plaques.

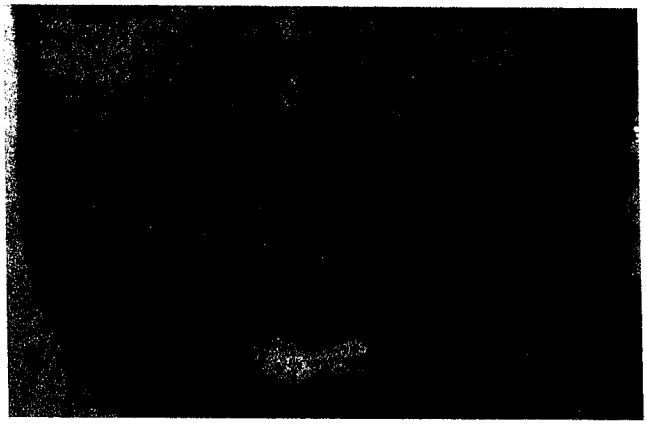

FIGURE 17. Discoid lupus erythematosus. This patient has hyperpigmented, raised patches with keratotic scaling and follicular plugging involving the malar and perioral areas as well as the bridge of the nose. Areas of atrophic scarring are also present.

underlying SLE when making therapeutic and prognostic decisions.

Painless oral or nasopharyngeal ulcerations occur in 5% of patients with SLE, with involvement of hard palate suggestive of the diagnosis. Rarely, DLE can be 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.

See MKSAP 18 Dermatology for more information.

Musculoskeletal Involvement

Joints are affected in 90% of patients with SLE. The most common involvement is polyarthralgia, with frank arthritis occurring in 40%. Typical distribution is small peripheral joints, but large joints are also affected. In contrast to rheumatoid arthritis, SLE arthritis is nonerosive, but reducible subluxation of the digits, swan neck deformities, and ulnar deviation (Jaccoud arthropathy) can occur.

A serious complication of SLE is osteonecrosis, which most commonly affects the hips but can also involve other large joints, and should be suspected when there is otherwise unexplained pain and/or reduced range of motion. Chronic prednisone doses (>20 mg/d), severe/active SLE, and vasculitis are all associated with increased risk. MRI is the modality of choice for sensitive evaluation of early disease, with plain radiography useful to diagnose and follow later stages. Small lesions can improve and resolve spontaneously, but larger lesions usually lead to bony collapse and structural sequelae.

Myalgia and subjective weakness are common; frank myositis is rare. Assessment is complicated by the potential effect on muscle of antimalarials (rarely) and glucocorticoids (commonly), which must be differentiated from active SLE disease. Fibromyalgia is a common comorbidity (30%); symptoms may be similar to active SLE disease.

Kidney Involvement

Kidney disease occurs frequently among patients with SLE (70%) and was the major cause of SLE mortality prior to the advent of dialysis. Lupus nephritis can present with minimal laboratory abnormalities (non-nephrotic proteinuria, hematuria), frank nephritis (hypertension, lower extremity edema, active urine sediment, and elevated serum creatinine), and/or nephrosis (nephrotic-range proteinuria, dependent edema, and thrombosis). Untreated active disease may progress to kidney failure.

All patients with SLE should be regularly evaluated for kidney disease by assessing serum creatinine and urine for

protein and microscopic evaluation. Patients with significant abnormalities, including proteinuria greater than 500 mg/24 h or active urine sediment, should be urgently evaluated for active disease. Anti-double-stranded DNA antibody titers are a marker for risk, and complement consumption is a common phenomenon during active kidney disease.

Kidney biopsy defines both the histological subtype and the activity/chronicity of disease and is usually essential to make therapeutic decisions. Indications for kidney biopsy include an otherwise unexplained rise in serum creatinine, proteinuria greater than 1000 mg/24 h, proteinuria greater than 500 mg/24 h with hematuria, or an active urine sediment.

Patients who have SLE with hypercoagulable states (for example, nephrosis or antiphospholipid syndrome) may be at risk for renal artery or vein thrombosis.

See MKSAP 18 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 and has 19 defined manifestations. NPSLE prevalence is high (75%), with the most common manifestations being headache, mild cognitive dysfunction, and mood disorder. Peripheral neuropathy occurs in 10% to 14% of patients. Severe acute presentations, including seizures and psychosis, happen infrequently (<5%) but require aggressive symptomatic as well as disease-specific treatment.

Patients with suspected 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 with suspected peripheral neuropathies, electromyography and nerve conduction studies should be performed. Neuropsychologic testing may help distinguish organic versus functional cognitive changes.

Cardiovascular Involvement

Asymptomatic pericarditis is the most frequent cardiac manifestation of SLE (40%). When symptomatic, features include chest pain, exudative effusion, and rarely tamponade or chronic constriction. Patients with SLE have a 2- to 10-fold increased prevalence of coronary artery disease (CAD), the most common cause of death among older patients. High SLE disease activity and prednisone doses greater than 10 mg/d are independent risk factors for future CAD.

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. Myocarditis occurs in 5% to 10% of patients with SLE and usually presents as insidious heart failure but can be acute.

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

The cytopenias 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 cytopenias require prompt evaluation with serologic studies and/or bone marrow biopsy. An exact cause of cytopenias may be difficult to ascertain, and a trial of medication adjustment in concert with evaluation for other causes is often necessary.

Antiphospholipid antibodies/lupus anticoagulant (APLA/LAC) are frequently present in patients with SLE (about 40%) and may be associated with a false-positive rapid plasma reagin test for syphilis. Most patients are asymptomatic.

CONT. Thrombotic events occur in about 30% and are associated with moderate or high titer of the antibodies; these include venous and arterial thrombosis, miscarriage, stillbirth, livedo reticularis, and cardiac valve thickening/vegetations. The highest risk of thrombosis occurs in the presence of triple positivity for LAC, anti-β_2-glycoprotein I, and anticardiolipin antibodies. Patients with SLE are at increased risk for thrombotic events even in the absence of APLA.

See MKSAP 18 Hematology and Oncology for more information.

Gastrointestinal Involvement

Gastrointestinal disease is a common (40%) and frequently 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. Patients with APLA can present with mesenteric thrombosis.

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 can develop 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.

- The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash) is characterized by erythema/edema over the cheeks and bridge of the nose, sparing the nasolabial folds.
- Polyarthralgia of the small peripheral joints is the most common joint manifestation in systemic lupus erythematosus; a nonerosive arthritis occurs in 40% of patients.
- All patients with systemic lupus erythematosus should be regularly evaluated for kidney disease by assessing 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.
- Patients with systemic lupus erythematosus (SLE) have a 2- to 10-fold increased prevalence of coronary artery disease (CAD); high SLE disease activity and prednisone doses greater than 10 mg/d are independent risk factors for developing CAD.

Association with Malignancy

The greatest malignancy risk among patients with SLE is non-Hodgkin lymphoma, presumably due to chronic B-cell activation and/or medications (azathioprine or cyclophosphamide). Other hematologic malignancies, including Hodgkin lymphoma and leukemia, are also increased. Lung cancer rates are increased slightly compared with the general population, probably related to smoking. Cervical cancer risk is increased, likely due to immunosuppression and increased prevalence of human papillomavirus.

- The greatest malignancy risk among patients with systemic lupus erythematosus is non-Hodgkin lymphoma.

Diagnosis

General Considerations

The diagnosis of SLE should be considered in any patient with unexplained symptoms affecting multiple organ systems or with any individual manifestation of SLE, especially in young women. At initial presentation, skin and joint manifestations are most common, along with constitutional symptoms (fever, weight loss, or severe fatigue). Patients with subjective complaints of fatigue, myalgia, and/or arthralgia, but lacking objective findings, most likely have an alternative diagnosis and should not be evaluated for SLE.

Classification criteria for SLE were developed by the American College of Rheumatology (ACR) in 1982 and revised in 1997; although intended for accruing homogenous SLE populations for research studies, they can also be used to suggest a clinical diagnosis of SLE (**Table 18**). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) proposed and validated alternative SLE classification criteria that are similar to the ACR criteria but require the following: 1) fulfillment of at least four criteria, with at least one clinical criterion and one immunologic criterion; or 2) biopsy-proven lupus nephritis as sufficient clinical criterion in the presence of ANA or anti-double-stranded DNA antibodies. When compared with the ACR classification criteria, the SLICC classification criteria are associated with fewer misclassifications and have greater sensitivity but less specificity.

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 methodology for testing ANA is the indirect immunofluorescence assay, which is highly sensitive (95%) for SLE. ANA tests should be interpreted in the context of the probability of disease because ANA may be present in other autoimmune diseases, and low-titer positivity may be seen with aging and even in healthy individuals.

If ANA is positive, 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

TABLE 18. American College of Rheumatology Criteria for the Classification of Systemic Lupus Erythematosus

Criteria[a]	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous, circular, raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Rash after exposure to ultraviolet light
Oral ulcers	Oral and nasopharyngeal ulcers (observed by physician)
Arthritis	Nonerosive arthritis of ≥2 peripheral joints, with tenderness, swelling, or effusion
Serositis	Sterile pleuritis, pericarditis, or peritonitis (documented by electrocardiogram, rub, or evidence of effusion or ascites)
Kidney disorder	Urinalysis: 3+ protein or urine protein >500 mg/24 h; cellular casts
Neurologic disorder	Seizures or psychosis (without other cause)
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/μL [4.0 × 10^9/L]) or lymphopenia (<1500/μL [1.5 × 10^9/L]) or thrombocytopenia (<100,000/μL [100 × 10^9/L]) in the absence of offending drugs
Immunologic disorder	Anti-double-stranded DNA, anti-Smith, and/or antiphospholipid antibodies
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in the absence of drugs known to induce ANA

ANA = antinuclear antibodies.

[a]Any combination of 4 or more of the 11 criteria, well documented at any time during a patient's history, makes it likely that the patient has systemic lupus erythematosus (specificity and sensitivity are 95% and 75%, respectively).

From Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. [PMID: 9324032] Copyright 1997, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

to further characterize the disease (**Table 19**). A small percentage of patients with SLE are negative for ANA but positive for anti-Ro/SSA antibodies. A negative ANA plus a negative anti-Ro/SSA essentially rules out SLE.

Disease activity markers (complements C3 and C4) should be assessed initially and regularly thereafter. Complement levels are reduced during SLE activity, reflecting immune complex formation and complement consumption. Anti-double-stranded DNA antibody levels may rise with SLE kidney disease activity. Other SLE autoantibodies, including the ANA test, do not reflect disease activity and need not be repeated. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are variably associated with disease activity; some patients with SLE do not generate CRP during SLE flares, which may be helpful in distinguishing flares from infection.

Differential Diagnosis

The differential diagnosis of SLE includes multisystem diseases, acute and chronic infections, medication effect, malignancies (particularly hematologic), and neurologic diseases (for example, 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).

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.

Certain medications can cause drug-induced lupus erythematosus (DILE), which mimics SLE (**Table 20**). The syndrome is usually mild with symptoms of malaise, fever, arthritis, and rash associated with a transient positive ANA and antihistone antibodies. Symptoms resolve after discontinuing the offending agent. Kidney and central nervous system disease are uncommon. Patients with SLE are at no more risk of DILE than the general population, and there is no contraindication to using medications associated with DILE in patients with SLE.

KEY POINTS: Clinical Presentation

- Patients with systemic lupus erythematosus typically initially present with skin and joint manifestations, along with fever, weight loss, or severe fatigue.
- 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.

(Continued)

KEY POINTS: Clinical Presentation (Continued)

- If antinuclear antibody testing is positive, 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 management requires close monitoring of disease activity and frequent adjustment of therapy. Pharmacologic therapy is almost always required and is usually directed toward specific organ involvement (**Table 21**).

Hydroxychloroquine should be initiated in every patient who can tolerate it, because evidence suggests it reduces disease-associated damage, prevents disease flares, and improves kidney and overall survival. Hydroxychloroquine can be used alone for mild disease (especially skin and joints) and in combination with other agents in severe disease. In addition, hydroxychloroquine may reduce the risk of thrombosis, liver

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-α 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.

TABLE 21. Medications Commonly Used to Treat Systemic Lupus Erythematosus

Medication	Common Uses in SLE	Important Side 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 all patients; 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.

disease, and myocardial infarction; improve lipid profiles; and improve outcomes in high-risk pregnancies.

Glucocorticoids are a mainstay of SLE management, 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 cytopenias, 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 followed by high-dose daily prednisone. After disease stability is achieved, glucocorticoids are tapered to the lowest effective dose, ideally to eventual discontinuation.

Immunosuppressive therapy is usually initiated concurrently with glucocorticoids to achieve and maintain disease control and to allow tapering of glucocorticoids. Intravenous cyclophosphamide is used as induction therapy for severe or refractory disease (for example, 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 currently 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 has been shown to be useful in skin/joint involvement and moderate/severe disease.

NSAIDs can be used as adjunct therapy for arthritis and pleuropericarditis, but are not disease modifying and may adversely affect kidney function and blood pressure.

See Principles of Therapeutics for information on SLE medication toxicities, monitoring parameters, and more. See MKSAP 18 Nephrology for details on the treatment of lupus nephritis.

KEY POINTS

- Hydroxychloroquine should be initiated in every patient with systemic lupus erythematosus who can tolerate it, because it can reduce disease-associated damage, prevent disease flares, and improve kidney and overall survival.
- Glucocorticoids are a mainstay of systemic lupus erythematosus management, particularly in acute disease; after disease stability is achieved, glucocorticoids are tapered to the lowest effective dose, ideally to eventual discontinuation.
- In systemic lupus erythematosus, immunosuppressive therapy is usually 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 APLA antibodies. The best time to consider pregnancy is when SLE is quiescent, and conception should be considered only after at least 6 months of adequate disease control.

Proteinuria may increase during pregnancy in patients with SLE, making distinction between SLE and preeclampsia/eclampsia a challenge. Increases in anti-double-stranded DNA antibody levels, 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 (CHB). Although the risk of CHB in the offspring of an anti-Ro/SSA-positive woman is only 2%, it is associated with significant fetal and neonatal morbidity and mortality. After a woman bears a child with neonatal lupus erythematosus, the risk of CHB is substantially increased (20%) in subsequent pregnancies. Hydroxychloroquine may reduce the overall risk.

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, which should be used only if absolutely necessary. Belimumab, methotrexate, mycophenolate mofetil, and cyclophosphamide should be avoided. Cyclophosphamide is associated with age- and dose-dependent infertility. See Principles of Therapeutics for information on medications and pregnancy.

- 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 considered 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 the pregnancy.

Prognosis

The prognosis in SLE has improved significantly, and there is now a 90% 5-year survival rate. Early mortality is usually related to SLE disease and infections, and late mortality related to cardiovascular disease. Factors adversely affecting survival include myocarditis, nephritis, low socioeconomic status, male gender, and age over 50 years at diagnosis. SLE tends to

be a chronic waxing and waning disease with only 2% of patients achieving remission at 5 years.

KEY POINT

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

Sjögren Syndrome

Epidemiology and Pathophysiology

Sjögren syndrome is an autoimmune exocrinopathy affecting salivary and lacrimal glands. It is more prevalent in women and white persons and commonly presents in the fourth and fifth decades. Primary Sjögren syndrome occurs in isolation; secondary Sjögren syndrome occurs in the setting of other rheumatologic diseases, most commonly rheumatoid arthritis and systemic lupus erythematosus. Whereas the prevalence of primary Sjögren syndrome ranges from 0.5 to 5 patients per thousand, secondary Sjögren syndrome is common (10%-30%) among populations with predisposing rheumatologic conditions. Sjögren syndrome etiology remains unclear, although genetic associations include several HLA subtypes.

Clinical Manifestations

The most common presentation of Sjögren syndrome is sicca, consisting of dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia). Patients report gritty eyes or a foreign body sensation. Oral dryness can cause caries and difficulty eating unmoistened food. Symmetric parotid and lacrimal swelling is common, as is skin and vaginal dryness.

Extraglandular manifestations may also occur (**Table 22**). Arthralgia and arthritis are common; the joint distribution and presentation resemble rheumatoid arthritis but without bone erosions (Jaccoud arthropathy). Patients with Sjögren syndrome are at increased risk for non-Hodgkin lymphoma, presumably related to chronic lymphocyte activation.

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, distal (type 1) renal tubular acidosis, glomerulonephritis: 5%-6%
Neurologic	Central nervous system (CNS): demyelinating disease, myelopathy, cranial nerve neuropathy
	Peripheral nervous system: small-fiber neuropathy, mononeuritis multiplex, peripheral neuropathy
	8%-27% for CNS and peripheral
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%)

TABLE 23. American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren Syndrome[a]

The presence of a subjective finding of Sjögren syndrome (e.g., sicca complaint) plus any combination of the following resulting in a score of ≥4:

Item	Score
Salivary gland biopsy with ≥1 foci of lymphocytic infiltrate/4 mm^2	3
Anti-Ro/SSA autoantibodies	3
Ocular staining score ≥5 in at least one eye	1
Schirmer test ≤5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 mL/min	1

[a]Exclusion criteria include prior head/neck radiation and history of active hepatitis C virus infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease.

From Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017 Jan;69(1):35-45. doi: 10.1002/art.39859. [PMID: 27785888]. Copyright 2016, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

Diagnosis

A diagnosis of Sjögren syndrome is typically triggered by a complaint of sicca and requires objective confirmation of exocrinopathy along with demonstration of autoimmunity (**Table 23**). Dry eyes can be assessed using the Schirmer test, in which a strip of filter paper is placed under the lower eyelid and wetting is measured; less than 5 mm in 5 minutes indicates dryness. More formally, dryness and corneal damage are ascertained by slit-lamp examination by an ophthalmologist using fluorescein and lissamine green dyes. Dry mouth is assessed by direct examination, with dental caries and a lack of saliva suggesting the diagnosis. Measurement of salivary flow (sialography) is easily done but is less commonly performed. Salivary gland imaging with MRI or ultrasonography may assist in identifying characteristic abnormalities and provide additional support for the diagnosis.