108 Systemic Lupus Erythematosus
James G. Adams

PERSPECTIVE
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with widespread physical effects caused by the production of autoantibodies to components of cellular nuclei. The term lupus (Latin for “wolf”) is attributed to the 13th-century physician Rogerius, who used it to describe the characteristic facial lesions that were reminiscent of a wolf’s bite.

In some patients the illness is mild. Other patients suffer early, catastrophic organ damage. Early deaths are frequently due to injury to the kidney and brain. Later deaths often occur as a result of acute myocardial infarction, stroke, or infection. Steroids used for treatment may cause or worsen complications.

Acknowledgment and thanks to Clare Sercombe for contributions to the first and second editions of this chapter.

KEY POINTS
- Systemic lupus erythematosus is an autoimmune disease that damages the skin, kidneys, bones, lungs, brain, and nearly every other organ in the body.
- The damage is due to inflammation as a result of a direct antibody reaction to body tissues, deposits of immune complexes, and secondary thrombosis.
- A characteristic finding is fever, malar rash, and joint pain in a young, premenopausal woman.
- Sunlight and certain viruses and drugs can induce an autoimmune response in a genetically susceptible host.
- Basic treatment of pain is with nonsteroidal antiinflammatory medications or steroids. Many patients additionally require immunosuppressants, antimalarial drugs, and other therapies prescribed by a rheumatologist.
- Patients with systemic lupus erythematosus have increased risk for serious infection, often because of the steroids and immunosuppressants required to treat the disease.
- Morbidity is due to organ failure, primarily of the kidney and brain.

EPIDEMIOLOGY
SLE is more common by a ratio of 12:1 in women aged 15 to 45 years and by a ratio of 2:1 in younger and older women. The overall prevalence of this disease is about 1 in 1000. In most studies of SLE, about 90% of enrollees are women. In the United States, the disease is three times more common in black women than in white women. In addition to genetic factors, age, sex, race, and socioeconomic status have an impact on disease expression and prognosis. With optimal management, the 20-year survival rate approaches 70% and the 1-year survival rate is about 90%.

PATHOPHYSIOLOGY
SLE is a prototypic autoimmune disease characterized by tissue damage from excessive antibody production and immune complex deposition. The chronic inflammation characteristic of the disease originates from overproduction of autoantibodies and failure of the body to suppress them.

Nearly every tissue in the body can be affected. Autoantibodies directly react to human antigens, immune complexes are deposited in tissue and blood vessels, and the complement cascade is activated, which results in inflammation and organ damage.

The exact cause is unknown, but genetic predisposition, viruses, ultraviolet light (including sunlight), and medications such as hydralazine, isoniazid, and procainamide are known to be involved in certain patients. There is a relationship to specific human leukocyte antigen genotypes.

Autoantibodies to lupus erythematosus are found in laboratory workers who handle lupus sera. Exposure to certain drugs can produce a SLE-like syndrome. Hormonal factors include an association with estrogens, which may explain the higher prevalence in women.

PRESENTING SIGNS AND SYMPTOMS
The triad of fever, joint pain, and rash in a woman of childbearing age suggests SLE. The most well-recognized cutaneous finding is the red, raised butterfly rash (Fig. 108.1), but malaise, fatigue, aches, fever, and weight loss are the most common symptoms. The rash, which does not cross the
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SKIN
The characteristic facial eruption, seen in up to 40% of patients, may be the first sign or may accompany flares of the disease. It can be exacerbated by exposure to ultraviolet light.

KIDNEYS
Clinical nephritis, defined as persistent proteinuria, develops in approximately 50% of patients with SLE, although mesangial and glomerular immunoglobulin deposition occurs in almost all patients. Usually, the nephritis does not cause any symptoms until it progresses to an advanced stage. Serum creatinine is an important but insensitive indicator of early renal disease because many nephrons must be damaged before the creatinine level is elevated. Renal complications are recognized by hematuria, proteinuria, and red blood cell casts. Active urine sediment with excretion of red blood cell casts and increasing proteinuria is cause for concern. Patients with active urine sediment may benefit from aggressive steroid or other immunosuppressive therapy. Indications for treatment include worsening renal failure, decreasing serum complement levels, increasing anti–double-stranded DNA levels, and nephritic urinary sediment, especially when accompanied by increasing or nephrotic-range proteinuria.

CENTRAL NERVOUS SYSTEM
Seizures, stroke, migraines, peripheral neuropathies, and psychosis are common. These symptoms may appear early but are rarely the initial sign of SLE. Central nervous system involvement develops in approximately 50% of patients with SLE. Full recovery from the neuropsychiatric manifestations occurs in approximately 70% to 85% of patients, although mortality from such events is 10% to 15%.

Seizures are the most frequent central nervous system manifestation. Strokes as a result of vascular inflammation and thrombosis are also common, especially in association with antiphospholipid syndrome. Cerebritis should be considered when a patient with SLE exhibits a change in behavior or altered mental status. Infection should also be considered, particularly in patients receiving immunosuppressive therapy. These patients are at risk for bacterial, fungal, and tuberculous infections, in addition to brain abscesses. A head computed tomography scan and lumbar puncture are generally required to clarify the diagnosis. Symptoms may range from subtle changes in behavior to frank psychosis. Steroids are an important therapy for patients who have lupus-associated cerebritis.

CARDIOVASCULAR SYSTEM
Pericarditis
Pericarditis is the most common heart-related problem and is reported to occur in 20% to 30% of patients, but it is present in up to 60% at autopsy. Electrocardiographic (ECG) findings

Clinical manifestations range widely from mild to life-threatening. About half of patients have severe disease, defined as complications that threaten life or organ function. Some rash or arthritis (or both) develops in a substantial majority of patients. At least half of patients have the Reynaud phenomenon, mucous membrane involvement, and renal or central nervous system involvement. About half of patients report photosensitivity. Pleurisy, vasculitis, or gastrointestinal involvement will develop in a quarter to a third of patients. Less common but important manifestations include pancreatitis, myositis, and myocarditis.
### BOX 108.1 Criteria for the Classification of Systemic Lupus Erythematosus*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Malar Rash</strong></td>
<td>Fixed erythema, flat or raised, over the malar eminences with sparing of the nasolabial folds</td>
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<tr>
<td><strong>Discoid Rash</strong></td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
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<td><strong>Photosensitivity</strong></td>
<td>Rash as a result of an unusual reaction to sunlight, as determined by the patient’s history or physician observation</td>
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<td><strong>Oral Ulcers</strong></td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by the physician</td>
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<tr>
<td><strong>Nonerosive Arthritis</strong></td>
<td>Involving two or more peripheral joints and characterized by tenderness, swelling, or effusion</td>
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<tr>
<td><strong>Pleuritis or Pericarditis</strong></td>
<td>Pleuritis: Convincing history of pleuritic pain or a rub heard by the physician or evidence of pleural effusion</td>
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<td>Pericarditis: Documented by electrocardiogram or rub or evidence of pericardial effusion</td>
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<tr>
<td><strong>Renal Disorder</strong></td>
<td>Persistent proteinuria greater than 0.5 g/day or greater than 3+ if a quantitative assay is not performed</td>
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<td>Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td><strong>Seizures or Psychosis</strong></td>
<td>Seizures: In the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)</td>
</tr>
<tr>
<td></td>
<td>Psychosis: In the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)</td>
</tr>
<tr>
<td><strong>Hematologic Disorder</strong></td>
<td>Hemolytic anemia with reticulocytosis</td>
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<tr>
<td></td>
<td>Leukopenia—less than 4000/mm³ on two occasions</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia—less than 1500/mm³ on two occasions</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia—less than 10,000/mm³ in the absence of offending drugs</td>
</tr>
<tr>
<td><strong>Immunologic Disorder</strong></td>
<td>Anti-DNA—antibody to native DNA in abnormal titers</td>
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<td></td>
<td>Anti-Sm—presence of antibody to Sm nuclear antigen</td>
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<td></td>
<td>Positive finding of antiphospholipid antibodies based on the following:</td>
</tr>
<tr>
<td></td>
<td>• Abnormal serum concentration of IgG or IgM anticardiolipin antibodies</td>
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<tr>
<td></td>
<td>• Positive test for lupus anticoagulant using a standard method</td>
</tr>
<tr>
<td></td>
<td>• False-positive test result for at least 6 months and confirmed by Treponema pallidum immobilization or a fluorescent treponemal antibody absorption test</td>
</tr>
<tr>
<td><strong>Positive ANA Test</strong></td>
<td>Abnormal ANA titers by immunofluorescence or an equivalent assay at any time in the absence of drugs</td>
</tr>
</tbody>
</table>

*Modified from Hochberg MC, Silman AJ, Smolen JS, editors. Rheumatology, vol 2. 3rd ed. London: Mosby; 2003, Chapter 122. ANA, Antinuclear antibody; anti-Sm, anti-Smith; IgG, immunoglobulin G; IgM, immunoglobulin M.

*Based on the American Rheumatism Association revised criteria for the classification of lupus. The criteria consist of conditions associated with systemic lupus erythematosus, including clinical symptoms, systemic complications, and diagnostic and laboratory test findings (see text for discussion).
alone may lead to the diagnosis because the pericarditis can be clinically inapparent. Alternatively, some patients will have fever, tachycardia, chest pain, and a cardiac rub. The pericarditis is usually fairly benign and responds well to ibuprofen or, in severe cases, to corticosteroids. Pericardial effusion, typically a transudative serous fluid, occurs in about 20% of patients. Tamponade is rare but has been noted. An uncommon but dangerous complication is purulent pericarditis, which should be suspected in patients who appear especially ill. Typical causes are Staphylococcus aureus and Mycobacterium tuberculosis. Purulent pericarditis is exudative with a high C-reactive protein level and elevated white blood cell count.

**Myocarditis**

Myocarditis is rarely diagnosed clinically but is found on autopsy in about 40% of patients. The 10% of patients in whom the diagnosis is made typically have symptoms that resemble those of cardiomyopathy, including congestive heart failure, ventricular dysrhythmia, tachycardia, and nonspecific ECG changes. Severe myocarditis should be treated with high-dose systemic corticosteroids, control of hypertension, and correction of volume overload.

**Endocarditis**

Libman-Sachs vegetations, present in up to 10% of patients with SLE, are growths on heart valves that usually cause no symptoms. Occasionally, these vegetations may be complicated by infection, valvular dysfunction, and rarely thromboembolism. The mitral valve is most commonly involved, although all four valves may have vegetations.

**Coronary Artery Disease and Coronary Vasculitis**

Accelerated atherosclerosis as a result of corticosteroid use may cause coronary ischemia. Mortality from coronary artery disease is seen in up to 30% of patients with SLE despite improved survival of patients with renal and cerebral SLE. Hypertension, smoking, and hypercholesterolemia significantly increase the risk for mortality in these patients. Patients with acute cardiac ischemia should be treated with standard interventions.

Coronary vasculitis is rare and best treated with steroids. Differences in treatment make the distinction between coronary vasculitis and coronary artery disease important. The diagnosis can be made by coronary angiography. Evidence of aneurysmal dilation of the coronary arteries is seen in patients with coronary vasculitis.

**Hypertension**

Between 25% and 50% of patients with SLE often have systemic hypertension as a result of lupus nephritis and steroid use.

**PULMONARY SYSTEM**

**Pleuritis**

Pleurisy and pleural effusions occur in more than half of patients with SLE. The pleural effusions are usually small and bilateral but can occasionally be very large. Pleural fluid is generally exudative, with glucose levels similar to serum glucose levels. In contrast, the pleural fluid of patients with rheumatoid arthritis has very low glucose levels.

**Pneumonitis**

Pneumonitis in patients with SLE causes diffuse interstitial infiltrates, although patients have usually had the disease for several years before they suffer from pneumonitis. Bacterial, fungal, and opportunistic infections must be considered before confirming the diagnosis, especially in patients taking immunosuppressive agents. Patients with SLE are particularly at risk for pneumococcal disease, in part because of autopsenectomy or splenic dysfunction.

**Pulmonary Fibrosis**

Chronic interstitial infiltrates leading to pulmonary fibrosis may also develop in patients with SLE. These patients need inpatient treatment, and their condition may progress to chronic hypoxia, pulmonary hypertension, and right-sided heart failure.

**Shrinking Lung Syndrome**

When a patient has shortness of breath, low lung volumes seen on a chest radiograph, and no other identifiable cause, shrinking lung syndrome is signaled. An elevated diaphragm but clear lung fields is characteristic. This syndrome may be chronic as a result of impaired respiratory mechanics, weak muscles, and poor diaphragmatic function. If the findings are acute, the patient may have a good response to steroids.

**GASTROINTESTINAL SYSTEM**

Mucous membrane lesions (small, shallow ulcerations in the mouth) occur in up to 19% of patients. Oral ulcerations usually accompany disease flares. Esophageal dysmotility is occasionally seen; however, it is much less common in patients with SLE than in patients with scleroderma.

Patients with intestinal pseudoobstruction may have crampy abdominal pain and a clinical and radiographic picture consistent with obstruction. They should be observed for resolution.

Mesenteric vasculitis is the most serious gastrointestinal complication. Patients have abdominal pain and, typically, bloody diarrhea along with evidence of vasculitis elsewhere. Bowel vasculitis may progress to perforation, gangrene, and peritonitis.

**HEMATOLOGIC DISORDERS**

Anemia, which affects up to 40% of patients with SLE, may result from hemolysis, drugs, renal disease, blood loss, or chronic disease. The most important cause is autoimmune hemolytic anemia. The Coombs test, which detects hemolysis caused by antibodies directed against red blood cell antigens, is usually positive.

Thrombocytopenia occurs in 25% of patients. Antiplatelet antibodies may be the cause of the low platelet count seen in patients with active SLE. Treatment of severe lupus-related thrombocytopenia is controversial; some authors advocate the use of vinca alkaloids and intravenous gamma globulin.

An important cause of thrombocytopenia is thrombotic thrombocytopenic purpura, which may be difficult to distinguish from acute autoimmune hemolysis. Patients with thrombotic thrombocytopenic purpura typically have low platelets, hemolytic anemia, central nervous system dysfunction, renal insufficiency, and fever. Symptoms can appear similar to those of a lupus flare. Treatment requires plasma exchange, so it is...
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**Table 108.1 Drugs Implicated in Lupuslike Syndromes**

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DRUG</th>
<th>RISK</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>Procainamide, quinidine, practolol†</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Hydralazine, methylldopa, reserpine</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Antihypertensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isoniazid, nitrofurantoin, penicillin, sulfonamides, streptomycin, tetracycline</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethosuximide, mephenytoin, phenytoin, primidone</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Antithyroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylthiouracil, propylthiouracil</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Psychotropic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine, lithium carbonate</td>
<td>Low</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aminoglutethimide, gold salts, α-penicillamine, phenylbutazone, methysergide</td>
<td>High</td>
</tr>
</tbody>
</table>


*Removed from the market because of lupuslike syndrome.

Important to either clinically distinguish or empirically initiate plasma exchange. Thrombotic thrombocytopenic purpura should be considered when a patient has a combination of microangiopathy, seizures, coma or altered mental status, and renal failure.

**DRUG-INDUCED LUPUS ERYTHEMATOSUS**

Procainamide has been known for more than 40 years to induce a lupus reaction. Since then, a large number of agents have been implicated, with hydralazine and procainamide being the most common (Table 108.1). The clinical manifestations vary, with most patients experiencing arthralgias and occasional pleuropedicardial pain. The full manifestations are present in less than 1% of patients taking high-risk drugs, although a positive antinuclear antibody titer can be found in more than 50%. Patients are generally women, middle-aged or older, and rarely African American, but this may be representative of the group of patients. The condition is usually reversible when drug therapy is stopped, with resolution occurring within days or weeks. Manifestations lasting for years have been reported. In patients with significant pleuropedicardial disease, a short course of tapered steroids has been used successfully once use of the implicated medication has been discontinued.

**TREATMENT**

Medical therapy attempts to reduce inflammation, suppress the immune system, and control pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressive agents are the mainstays of treatment. Aspirin and other NSAIDs are the primary treatment of arthralgias, pleurisy, and pericarditis. The maximum standard recommended doses of these agents are usually needed. These agents should be avoided in patients with severe gastrointestinal complications, renal insufficiency, nephritis, or thrombocytopenia. Treatment with NSAIDs can worsen lupus nephritis, either by causing interstitial nephritis or by inhibiting prostaglandins.

Topical corticosteroids control most rashes. Although anti-inflammatory and antimalarial drugs are often advocated for patients with minor symptoms to avoid the long-term complications of corticosteroid therapy, symptoms such as arthralgias, fatigue, pleurisy, and others may require lower-dose steroids, such as prednisone (0.5 mg/kg or less).

High-dose steroids (e.g., 1 mg/kg/day of prednisone or 1 g of methylprednisolone intravenously [IV]) are used when major organs are involved and also for hemolytic anemia and severe thrombocytopenia. For example, in patients with lupus-related cerebritis or acute worsening of lupus nephritis, 1 g/day of methylprednisolone IV may be given for several days.

Corticosteroids are associated with well-known complications, including steroid-induced diabetes, osteoporosis, weight gain, pancreatitis, osteonecrosis, accelerated atherosclerosis, and immunosuppression. Patients receiving chronic steroid therapy should be evaluated promptly for any episode of fever or potential infection. When patients who are taking corticosteroids have an acute serious illness or other physiologic stress (e.g., surgery, childbirth), they should also be given hydrocortisone (100 mg IV every 8 hours). Patients with overwhelming sepsis or shock should be given stress-dose steroids (e.g., 100 mg of hydrocortisone IV), in addition to the usual treatment with broad-spectrum antibiotics and intravenous resuscitation fluid.

Antimalarial drugs are effective for the cutaneous and musculoskeletal manifestations of SLE. Hydroxychloroquine and chloroquine are given on an outpatient basis in a loading dose for 4 weeks, followed by maintenance dosing once the symptoms are under control. Withdrawal of the drug may result in flare of the disease.

Immunosuppressive agents (azathioprine, methotrexate, cyclophosphamide) are reserved for patients with severe renal or cerebral disease in whom other therapies have failed and for patients who cannot tolerate corticosteroids. Studies of the use of immunosuppressants have shown decreased chronic renal scarring and a reduced likelihood of end-stage renal disease without an increase in mortality. The toxic effects of such drugs are numerous and include myelosuppression, risk for neoplasms, and infections, especially with gram-negative organisms, encapsulated gram-positive organisms, herpes zoster, and opportunistic organisms. Febrile patients who are taking azathioprine, methotrexate, or cyclophosphamide should be admitted regardless of whether a source is evident because gram-negative or streptococcal sepsis occurs in this population. Immunosuppressed patients with localized herpes zoster should be admitted for intravenous acyclovir treatment to prevent viral dissemination.

**FOLLOW-UP, NEXT STEPS IN CARE, AND PATIENT EDUCATION**

Patients with known disease and increasing arthritic pain or with a mild flare and no fever may be treated with NSAIDs...
SLE predisposes patients to anemia and thrombocytopenia. Patients should be admitted if there is evidence of active hemolysis with decreased hematocrit levels or hemolysis that is evident on the blood smear. Patients with thrombocytopenia should be admitted if evidence of bleeding is seen or if platelet counts are severely decreased (<50,000/mm³). If the patient is actively bleeding, platelet transfusion is appropriate; however, rapid destruction of the platelets may occur. Simultaneous administration of intravenous corticosteroids and gamma globulin will aid in increasing the platelet count and decreasing the amount of platelet destruction.

Patients with evidence of arterial or venous thrombosis should be admitted for anticoagulation and possible embolectomy. Anticoagulation can be achieved acutely with heparin, although large doses are occasionally needed to overcome the antibody effect. The partial thromboplastin time (PTT), if not elevated, can be monitored to assess for evidence of adequate anticoagulation, with careful observation for bleeding in patients who are also thrombocytopenic. Otherwise, patients with a prolonged PTT and evidence of lupus anticoagulant can be monitored with thrombin times if necessary. Patients with an international normalized ratio of less than 2.5 should nevertheless be considered to have a possible thrombus if they have a history of antiphospholipid syndrome.

Pregnant patients should undergo early follow-up with a high-risk obstetrician. Emergency delivery for a pregnant patient with SLE should include stress-dose steroid administration and close observation of the neonate for congenital complete heart block (i.e., neonatal lupus). Emergency cardiac pacing may be necessary for the infant.

**REFERENCES**

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES