



Outpatient management of systemic lupus erythematosus

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SUMMARY Systemic lupus erythematosus (SLE) is often managed by primary care practitioners, who must coordinate the care with the support of subspecialists. The management of patients with such a serious and chronic disease can be both rewarding and challenging. This article reviews common problems and suggests management strategies.

KEY POINTS Measurement of serum antinuclear antibodies can lead to an erroneous diagnosis if used as the sole basis for diagnosis. ■ Infections are the leading cause of death in lupus patients, and immunizations and antibiotic prophylaxis need to be considered. ■ Acute cutaneous SLE is exacerbated by exposure to ultraviolet light. Patients should avoid sun exposure. Specific treatment of cutaneous SLE includes topical corticosteroids and antimalarial agents. ■ Some of the most perplexing problems seen in SLE relate to neuropsychiatric features. ■ NSAIDs, corticosteroids, and antimalarials are the most commonly used medications for SLE.

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SYSTEMIC LUPUS Erythematosus (SLE, or simply “lupus”) is a systemic autoimmune disorder of unknown etiology that has protean manifestations. Patients commonly have involvement of the skin, joints, heart, lungs, kidneys, blood, digestive tract, and nervous system. Accurate diagnosis is made by careful evaluation of historic, physical, and laboratory findings. The incidence is estimated at 1.8 to 7.6 cases per 100 000. Women are affected nine times more often than men—and black women twice as often as white women.¹ For many patients, primary care physicians make the diagnosis and undertake the care, consulting rheumatologists when they encounter problems. Because SLE is not a simple disease, its management often does not permit a simplified approach. This article reviews the outpatient management of SLE.

DIAGNOSING SLE

Because of the profound medical, social, and psychological implications of having SLE, its diagnosis should not be made casually. The American College of Rheumatology

TABLE 1
CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*

Finding (at least four needed for diagnosis)	Comments
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	
Oral ulcers	Includes oral and nasopharyngeal, observed by physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness swelling, or effusion
Serositis	Pleuritis or pericarditis documented by electrocardiography or rub or evidence of pericardial effusion
Renal disorder	Proteinuria > 0.5 g/day or > 3+, or cellular casts
Neurologic disorder	Unexplained seizures or psychosis
Hematologic disorder	Hemolytic anemia or leukopenia (< 4000/mm ³) or lymphopenia (< 1500/mm ³) or thrombocytopenia (< 100 000/mm ³) in the absence of offending drugs
Immunologic disorder	Positive lupus erythematosus cell preparation, or anti-DNA or anti-Sm antibodies, or false-positive serologic test for syphilis
Antinuclear antibodies	An abnormal ANA titer by immunofluorescence or an equivalent assay at any time in the absence of drugs known to induce ANAs

*Adapted from Tan et al, reference 2

has published criteria for the classification of SLE (Table 1).² Though designed for population-based studies, these criteria provide a standardized approach to diagnosing SLE that is accurate if one considers the recognized inclusions, exclusions, and limitations.²

The serum antinuclear antibody (ANA) titer, a sensitive but nonspecific test for SLE, can lead to an erroneous diagnosis if used as the sole criterion. ANAs are produced in a variety of pathologic conditions unrelated to SLE (eg, other autoimmune connective diseases, chronic infections, drugs, neoplasia, chronic liver disease)—and in 5% to 10% of healthy people.³ A positive serum ANA titer is most helpful in confirming a diagnosis of SLE, because ANA-negative SLE is rare. Ninety-eight percent of patients with SLE have a positive ANA titer using the Hep-2 substrate.⁴ If a patient has had a positive titer, repeat testing has little value, since the ANA titer correlates poorly with disease activity.

Drug-induced SLE

A variety of medications can induce SLE. The most common are hydralazine, procainamide, chlorpromazine, methyl dopa, D-penicillamine, quinidine, and isoniazid, although more than 50 other drugs have also been implicated. A number of other drugs

can exacerbate the disease, including hormones, antibiotics, gold salts, and nonsteroidal anti-inflammatory drugs (NSAIDs).⁵ Although many of these drugs commonly induce positive ANA titers (up to 100% of patients treated with procainamide), far fewer patients actually develop disease.⁵ Drug-induced SLE tends to produce symptoms of fever, arthritis, rash, and serositis but spares major organ systems such as the kidneys and brain. Serologic testing of patients with drug-induced SLE often demonstrates antihistone antibodies in the absence of other lupus-specific autoantibodies (eg, anti-nDNA, anti-Sm). The disease usually remits after discontinuation of the offending drug, and immunosuppressive therapy is not usually required. NSAIDs may be used for symptomatic therapy.

MANAGING THE MANIFESTATIONS OF SLE

Most patients with SLE lead productive and useful lives; however, it is a chronic disease of frequent remissions and exacerbations that cause the patient to seek a physician's help. SLE can involve any organ system, but most signs and symptoms are not medical emergencies and can be managed in the outpatient setting. Patients with lupus need general health maintenance—and attention to their special prob-

lems. The patient-physician relationship should include ongoing patient education about basic aspects of the disease, the patient's role in its management, and its impact on activities of daily living.

Nonspecific systemic features

Nonspecific systemic features of SLE include fatigue, fever, and malaise. Most patients (82%) experience fatigue, which is often the patient's most disabling symptom.⁶ It may be the first symptom to appear and the last to leave. Treatment is problematic but involves sufficient rest and attention to other lupus-related problems, including associated fibromyalgia. Because physical and psychological stress may exacerbate lupus, measures that promote general well-being, such as good nutrition, rest, and physical conditioning, should be emphasized.⁷

Infections are the leading cause of death in lupus patients, and immunizations and antibiotic prophylaxis need to be considered.⁸ Except for live-virus vaccines in patients receiving corticosteroids or cytotoxic agents, vaccinations are safe and should be given according to guidelines established for the general population. Some physicians recommend antibiotic prophylaxis before dental and urologic procedures.⁹

Dermatologic manifestations

Perhaps the most obvious and troubling features to both patients and physicians are the dermatologic manifestations, which are wide-ranging and involve the skin, hair, and nails.¹⁰ The classic butterfly rash indicates acute cutaneous SLE and is greatly exacerbated by exposure to ultraviolet light. One third of lupus patients are photosensitive and should avoid sun exposure by wearing protective clothing and sunscreens. Even brief sun exposure can trigger systemic and cutaneous flares of SLE. Medications such as sulfonamides, thiazides, and tetracyclines can enhance photosensitivity and thus exacerbate sun-induced lesions.¹¹

Specific treatment of cutaneous SLE often includes topical corticosteroids and antimalarial agents (hydroxychloroquine, chloroquine, and atabrine). The dosage of hydroxychloroquine, the most frequently used antimalarial agent, should generally not exceed 6 mg/kg per day, owing to a small risk of ocular toxicity. All patients receiving these agents should have ophthalmologic follow-up every 6 to 12 months. Intralesional corticosteroids are also helpful for discoid lupus and well-circumscribed ar-

reas of alopecia. Diffuse alopecia is a particularly troubling cosmetic feature that, on rare occasions, requires specific therapy with corticosteroids. Although cutaneous exacerbations do not necessarily signify systemic exacerbations, the appearance of purpura, bullous lesions, and other vasculitic lesions should prompt an expeditious evaluation for associated systemic involvement.

Musculoskeletal manifestations

Almost all SLE patients experience musculoskeletal problems, ranging from fibromyalgia to myopathy. Fibromyalgia is common and is characterized by diffuse muscle aching without objective weakness and by nonrestorative sleep and well-defined trigger points.¹² Fibromyalgia is not a myopathy, and the presence of true muscle weakness should prompt a search for myositis and myopathy induced by medications such as corticosteroids or antimalarial drugs. Treatment of fibromyalgia includes empathetic physician-patient communication, aerobic exercise, and judicious use of agents to promote better sleep patterns. Short courses of cyclobenzaprine and tricyclic antidepressants in low doses are often useful, but their long-term use has not proven successful.¹³ Most patients have chronic symptoms that can be a considerable source of frustration to the physician and patient.

The joint symptoms in SLE are usually arthralgias and, less commonly, observable joint swelling and limitation of motion. Joint deformities may occur but are due to ligamentous laxity (Jaccoud's arthropathy) and usually do not involve destructive, erosive arthropathy. The mainstays of treatment are NSAIDs and physical therapy. Hydroxychloroquine is very useful in patients who do not respond to NSAIDs; corticosteroids should be reserved for symptoms unresponsive to these measures.

Cardiopulmonary manifestations

SLE frequently affects the heart and lungs, and manifestations range from mild serositis to overt organ failure. Symptoms related to serositis are common and usually involve pleuritis and pericarditis. Pleuritis is the most common pulmonary manifestation; however, one must be aware of uncommon presentations, including acute lupus pneumonitis, pulmonary hemorrhage, and diffuse interstitial lung disease.¹⁴ The latter are usually best managed in conjunction with an appropriate subspecialist.

Pleuritis often presents with shortness of breath and chest pain without radiographic evidence of

pneumonia. Significant pleural effusions can be seen on chest roentgenography, and care must be taken to exclude an infectious cause of infiltrates or effusions before proceeding with treatment. Pericarditis also manifests with chest pain and audible friction rubs. Pericardial effusions are often present but rarely lead to tamponade.¹⁵

Mild pericarditis and pleuritis are treated with NSAIDs; more severe cases often require moderate doses of corticosteroids. Other cardiac problems encountered include valvular abnormalities, conduction disturbances, premature atherosclerosis (especially in premenopausal women receiving corticosteroid therapy), and less commonly, overt myocarditis. The history and physical examination are usually helpful in differentiating pericarditis from other causes of acute cardiac symptoms; however, the evaluation may require further cardiovascular diagnostic testing.

Gastrointestinal manifestations

Gastrointestinal manifestations can be diverse, but the practitioner must be able to distinguish potentially catastrophic problems from less urgent conditions. Over the course of their illness, many lupus patients will have oral ulcers, NSAID-induced dyspepsia, nausea, or diarrhea. Treatment is largely symptomatic and, for oral lesions, includes topical corticosteroids and anesthetics if there is no evidence of oral infection or thrush. NSAID-induced dyspepsia can be managed symptomatically with H₂-blockers and reassessment of the need for continued NSAID use. The management of suspected NSAID gastropathy was recently reviewed by Loeb et al.¹⁶

Because lupus patients are immunocompromised by their underlying disease as well as by their medications, even subtle abdominal signs and symptoms should be considered as evidence of more severe problems. Ambiguous presentations may represent peritonitis (noninfectious, infectious, vasculitic), hemorrhage, ileus, or a perforated viscus. Lupus can affect any organ of the gastrointestinal system. Abdominal serositis is a troubling manifestation of SLE because it is often difficult to differentiate from an acute abdomen. Peritoneal fluid is often present and has a broad differential diagnosis.¹⁷ Massive ascites is most unusual. Once infection and other causes have been excluded, treatment consists of corticosteroids.

Hematologic abnormalities

Some of the most commonly encountered clinical problems involve hematologic abnormalities.

All hematopoietic cell lines can be affected, lymphocytes most commonly. Lymphopenia often requires no specific treatment. Thrombocytopenia not due to medications or concomitant illness is usually immune-mediated and generally does not need treatment unless associated with bleeding or if the platelet count falls below 50 000/mm³. Anemia is commonly observed and is usually due to chronic disease. A thorough evaluation will rule out blood loss, and, in the setting of an abnormal peripheral blood smear or red blood cell indices, should include an evaluation for autoimmune hemolytic anemia (Coomb's-positive or negative).

Treatment of acute immune-mediated thrombocytopenia or hemolytic anemia involves corticosteroids in high doses, which usually provide a good response. This response may be delayed, and short-term interventions such as transfusions may need to be considered, depending on the response to treatment. Patients unresponsive to this therapy should be referred for further evaluation and possible treatment with other agents, including cytotoxic drugs, danazol, and intravenous gamma globulin. Splenectomy is reserved for extreme, unresponsive cases, as it is frequently ineffective and can be associated with significant morbidity due to infections. Marrow suppression can be a feature of SLE, but also may be caused by medications (eg, cytotoxic agents).

Renal disease

Renal involvement, ranging from benign proteinuria to necrotizing glomerulonephritis and renal failure, affects half of all lupus patients.¹⁸ All lupus patients, even if free of symptoms, need periodic screening for renal involvement as manifested by increased serum creatinine, decreased creatinine clearance, proteinuria, or cellular casts. Patients with significant renal involvement should be managed with the help of a nephrologist. Underlying medical illnesses such as diabetes or hypertension, as well as various medications, can cause kidney dysfunction. In particular, coexisting hypertension can compound renal (and cardiac) disease and requires vigorous management.

Antiphospholipid antibody syndrome

The secondary antiphospholipid antibody syndrome is well recognized in patients with SLE. Approximately 40% of patients with SLE have antiphospholipid antibodies, and 25% of patients with these antibodies will have the antiphospholipid anti-

body syndrome.¹⁹ Patients with the syndrome have antibodies to negatively charged phospholipids (such as cardiolipin) and may have thrombosis. Laboratory abnormalities can include a prolonged partial thromboplastin time, a biologic false-positive test for syphilis (eg, the rapid plasma reagin [RPR] and the Venereal Disease Research Laboratory [VDRL] tests), and positive enzyme-linked immunosorbent assay (ELISA) tests for anticardiolipin antibodies.

The major clinical features are venous or arterial thrombosis (eg, deep venous thrombosis, pulmonary embolism, stroke), recurrent spontaneous abortions, and thrombocytopenia. Other associated phenomena include livedo reticularis, cardiac valvular abnormalities, and central nervous system disorders.

Patients with the antibody but not the syndrome should be treated prophylactically with aspirin if this is not contraindicated. Those with the syndrome require continuous anticoagulation with heparin, followed by warfarin. The target international normalized ratio is approximately 3.0. The efficacy of corticosteroids and cytotoxic drugs has not been established. Several studies have demonstrated that patients with the syndrome who take combination regimens of heparin, aspirin, or corticosteroids can successfully bear children.²⁰

Managing pregnancy and SLE

SLE does not generally affect fertility. Whether pregnancy causes inactive SLE to flare is controversial; however, flares are common during pregnancy and are more likely if the disease has been active recently.²¹ During pregnancy, maternal non-lupus-related problems (eg, pre-eclampsia, hypertension) and fetal wastage are more common among lupus patients than among mothers without lupus. Fetal wastage has many causes, including activity of maternal disease at conception, renal disease, and antiphospholipid antibody syndrome; a history of fetal losses increases the risk.²¹

Pregnant women with lupus should be managed as high-risk obstetric patients, and need close control of their SLE during this period. All medications need to be carefully reconsidered for possible adverse maternal and fetal effects and balanced with the need to control maternal disease. Cyclophosphamide and methotrexate are teratogenic and should be discontinued. It is unclear if hydroxychloroquine poses a significant risk, but the consensus is to discontinue it during pregnancy. Azathioprine can be used with caution during pregnancy. Pred-

nisone does not cross the placenta as much as other corticosteroids and is not contraindicated. NSAIDs should be avoided. Corticosteroid-treated patients should be given stress dosages (eg, hydrocortisone 100 mg intravenously every 8 hours) during delivery because of the risk of secondary adrenal suppression. The pediatrician needs to be alerted for the possibility of neonatal lupus, including cutaneous lesions and congenital heart block.

Neuropsychiatric features

Perhaps the most perplexing problems seen in SLE relate to neuropsychiatric features. A wide variety of psychiatric disturbances are encountered, including adjustment reactions, neurosis, psychosis, and organic brain dysfunction manifesting as defective learning, memory, and other cognitive functions. The problem is compounded by the presence of a potentially life-threatening disease, its impact upon the family, and medications that can alter the sensorium (eg, corticosteroids, NSAIDs). Consultation with a psychotherapist is often helpful, as is judicious use of psychiatric medications. Patients should be encouraged to learn more about their disease and to participate in self-help groups such those sponsored by the Lupus Foundation of America.

Neurologic presentations in lupus are as diverse as the psychiatric presentations. Virtually any neurological symptom or syndrome can be associated with SLE. The most commonly encountered are seizures, strokes, aseptic meningitis, headaches, and motor and sensory neuropathies. These problems are usually attributed to SLE, although care must be taken to exclude other possible causes such as infection, atherosclerosis, toxicities, or medications. The evaluation is often similar to that performed in patients who do not have SLE and can include lumbar punctures, electrodiagnostic testing, and imaging studies.²² Treatment often consists of that routinely used for the neurologic disorder as well as for a lupus flare. Patients may not improve until the underlying lupus is controlled. Steroids are routinely used for central nervous system involvement although their efficacy is not firmly established. Cytotoxic medications are reserved for those with serious disease that is unresponsive to corticosteroids.²³

Associated autoimmune disorders

SLE is frequently seen in association with other autoimmune disorders (overlap syndromes) such as mixed connective tissue disease, Hashimoto's thyroiditis, and Sjögren's syndrome, and rarely with

TABLE 2
MEDICATIONS FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Class	Drugs	Dosage
Nonsteroidal anti-inflammatory drugs*	Ibuprofen	Up to 3200 mg/day, in 3 or 4 divided doses
	Indomethacin	Up to 200 mg/day in 3 or 4 divided doses
	Naproxen	500–1500 mg/day, in 2 divided doses
Salicylates [†]	Aspirin	2.6–7.8 g/day, in 3 or 4 divided doses
	Diflunisal	500–1500 mg/day, in 2 or 3 divided doses
Antimalarials [‡]	Hydroxychloroquine	200–400 mg daily, up to 6 mg/kg/day
	Chloroquine	250 mg/day
	Quinacrine	50–100 mg/day
Glucocorticoids [§]	Prednisone	1–2 mg/kg/day in divided doses every 8 hours; rapidly consolidated to one dose daily and tapered as disease permits, preferably to less than 15 mg/day in the morning
	Methylprednisolone	0.8–1.6 mg/kg/day (see above); can be given as intravenous bolus 1 g on 3 consecutive days
	Hydrocortisone	4–8 mg/kg/day (see above)
Cytotoxic agents [§]	Azathioprine	1.25–2.5 mg/kg/day
	Cyclophosphamide	0.75 g/m ² intravenously, no more frequently than every 30 to 60 days

*Toxic side effects such as liver damage, aseptic meningitis, and renal impairment are especially frequent in SLE

[†]Monitor salicylate level; salicylates are no longer commonly used, as they have been superseded by nonsteroidal anti-inflammatory drugs

[‡]Owing to a small risk of ocular toxicity, all patients receiving these agents should see an ophthalmologist at least once a year

[§]For severe disease only; cytotoxic agents should be prescribed only by physicians familiar with their use

diseases such as scleroderma, polymyositis, or myasthenia gravis. Sjögren's syndrome can be a prominent feature of many patients who complain of dry mucosal surfaces (keratoconjunctivitis sicca and xerostomia). Symptomatic treatment is usually sufficient: frequent use of artificial tears and mouth rinses and avoidance of medications with anticholinergic effects.

DRUG THERAPY

A variety of proven and experimental therapies are available to treat SLE. Most commonly used in the outpatient setting are NSAIDs, corticosteroids, and antimalarials (Table 2). Cytotoxic agents should be prescribed only by those who have experience with them.

NSAIDs

In addition to the well-described NSAID complications such as dyspepsia and gastrointestinal bleed-

ing, certain other side effects are important to remember when treating lupus patients. Ibuprofen (and probably other NSAIDs) has been associated with the development of aseptic meningitis, and one needs to consider this possibility in patients presenting with headache or other neurological manifestations.²⁴ Like other medications, NSAIDs can also cause changes in the sensorium that complicate the evaluation of neuropsychiatric lupus. By causing renal dysfunction, NSAIDs can confound the clinical picture in established lupus nephritis. Periodic assessment of the complete blood count and renal and liver function should be performed in all patients receiving NSAIDs long-term.

Corticosteroids

Owing to the myriad toxicities of corticosteroids, they are reserved for patients in whom the benefits clearly outweigh the risks. The hazards associated with corticosteroid use dictate that they should be

used judiciously. Complications of long-term use include exacerbation of underlying diseases such as diabetes mellitus and hypertension, premature atherosclerosis, hypercortisolism, increased incidence of infection, cataract formation, osteonecrosis, and corticosteroid myopathy. Osteoporosis can be a major problem in patients treated long-term, and preventive strategies should be employed such as replacement estrogens, supplemental calcium, and modification of other risk factors, if possible.

If corticosteroid therapy is necessary, it is prudent to taper it as quickly as possible to the lowest dose necessary to control disease. Low doses, alternate-day doses, and short-term use are preferable when the clinical situation permits, as these may limit toxicity.

Antimalarial agents

Antimalarial agents are generally safe and cause few side effects. Hydroxychloroquine is used most commonly, followed by chloroquine. Atabrine is rarely used in this country because it is not widely available. Because patients usually require 2 to 4 months of treatment with these agents before they show improvement, concurrent treatment with other medications, such as NSAIDs, is often needed. A few patients treated with antimalarial agents experience dyspepsia, abdominal cramping, and diarrhea. These symptoms usually respond to dosage reduction and do not preclude long-term use. Adverse cutaneous reactions include pigment changes in the nails and skin, rashes, and dryness. Retinopathy is the most feared complication, though it is very rare in patients receiving less than 6.5 mg/kg/day of hydroxychloroquine. Fewer than 5% of patients receiving 400 mg per day of hydroxychloroquine develop corneal deposits, which are almost always asymptomatic.²⁵ Corneal deposits and early retinal changes confined to the macula disappear with drug discontinuance. More advanced retinal disease can result in irreversible visual loss. To avoid this, a baseline ophthalmologic examination is recommended, with follow-up every 6 to 12 months.²⁵

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