INSTRUCTIONS
The following article, "Approach to the Management of Systemic Lupus Erythematosus," is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 62.

OBJECTIVES
After participating in the CME activity, primary care physicians should be able to:
1. Understand the epidemiology and hormonal, genetic, and environmental triggers of systemic lupus erythematosus (SLE)
2. Recognize the common clinical presentations of SLE
3. Be familiar with therapy options for mild-to-moderate SLE
4. Be aware of both treatment and SLE complications
5. Understand the role of the rheumatologist and other specialists in SLE management

INTRODUCTION
Systemic lupus erythematosus (SLE) is the classic example of a multisystem autoimmune disease. It is characterized by the development of antibodies to cell nuclei, leading to a wide range of clinical manifestations. It is estimated that 500,000 to 2 million persons in the United States are affected by SLE. The most recent population-based study found that the incidence of SLE has tripled in the past 4 decades, from an average rate of 1.51 per 100,000 persons during 1950–1979 to 5.56 per 100,000 during 1980–1992. This increase cannot be attributed to an increase in the diagnosis of milder SLE because the frequency of lupus nephritis, a manifestation of more severe disease, has remained relatively constant throughout this period [1].

Often fatal in the 1950s, SLE has now become a manageable chronic disease due to improvements in diagnosis and treatment. Recognition that corticosteroids contribute greatly to later damage has led to the greater use of steroid-sparing immunosuppressives and to more careful monitoring to detect organ damage early. However, many challenges remain in improving survival, limiting organ damage, and improving quality of life for these patients. Although specialty care by a rheumatologist or nephrologist is often required, mild-to-moderate SLE can be managed successfully by primary care physicians. Therefore, it is important for physicians to be able to recognize the diverse manifestations of SLE and be able to initiate appropriate treatment. This article discusses evaluation methods and presents an approach to treatment that targets the disease manifestations and complications of the individual patient.

CASE STUDY
Initial Presentation
A 21-year-old female college student accompanied by her boyfriend and parents presents to her primary care physician with a chief complaint of fatigue and fevers that have led her to drop out of school.

History
The patient reports that her present illness began the previous summer. After a trip to the beach, she noted a rash on her face and some hair thinning and then became troubled by daily fevers and constant fatigue. She controlled the fevers with acetaminophen and ibuprofen. After starting college in September, she began to have joint pain that made walking to class difficult. She saw a nurse practitioner at the university health services center, who increased the ibuprofen dose to 800 mg 3 times daily. In early November, the patient decided to leave school and return home.

Current medications include acetaminophen, ibuprofen, and an oral contraceptive pill. The patient’s past medical history is unremarkable. Family history is notable for Hashimoto’s thyroiditis in her mother and a maternal cousin who may have rheumatoid arthritis. The patient is sexually active. She smokes 1 pack of cigarettes per day.

Physical Examination
Physical examination reveals a chronically ill-appearing young
What are the clinical features of SLE?
How is the diagnosis of SLE made?
What is the role of laboratory testing in patients with SLE?

Clinical Features
SLE is an especially challenging condition to recognize because it can present in virtually any organ system. The 3 most common presentations are lupus arthritis, cutaneous lupus, and renal lupus.

Lupus arthritis presents similarly to rheumatoid arthritis; it begins with joint stiffness that occurs particularly in the morning (called gel phenomenon) and arthralgias and eventually progresses to symmetric synovitis, initially in the small joints of the hands and wrists. Rheumatoid nodules are rarely seen. Eventually, other joints can also be affected, including the elbows, shoulders, knees, and ankles.

Cutaneous lupus is usually photosensitive. The malar rash is the classic example of cutaneous manifestations in SLE but must be differentiated from acne rosacea, seborrheic dermatitis, actinic telangiectasias, and steroid plethora. Other lupus rashes include discoid lupus and subacute cutaneous lupus. Discoid lupus is a deeper inflammatory rash that can heal with hypopigmentation or hyperpigmentation and scarring. Subacute cutaneous lupus is rare and is sometimes initially misdiagnosed as psoriasis or fungal infection. Oral and/or nasal ulcers are frequently found.

Lupus nephritis may be asymptomatic initially, and laboratory testing is necessary to detect it. Screening tests for lupus nephritis include a measurement of the serum creatinine and urinalysis with dipstick and microscopic analysis. If results of these tests are abnormal, urinalysis over 24 hours to measure creatinine clearance and total protein excretion are necessary. More than 50% of white patients with SLE and as many as 75% of African American patients with SLE will eventually have evidence of lupus nephritis.

Other clinical features of lupus include serositis, hematologic lupus, and neurologic lupus. Serositis can present as pericarditis, pleurisy, or abdominal serositis. Hematologic lupus presents as hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia. Neurologic lupus includes seizures and psychosis, but lupus can also cause organic brain syndrome (encephalopathy), cognitive function deficits, coma, stroke, transverse myelitis, cranial neuropathy, mononeuritis multiplex, and peripheral neuropathy.

Diagnosis
The presence of 4 of 11 American College of Rheumatology (ACR) criteria (Table 1) are needed to classify a patient as having SLE for research purposes [2,3]. The ACR classification criteria were not meant as diagnostic criteria, although they are sometimes used for that purpose. A patient can certainly be diagnosed as having SLE and not meet 4 criteria. For example, a patient with nephrotic syndrome and lupus nephritis on renal biopsy, positive test for antinuclear antibody (ANA), and low complement levels has SLE but meets only 2 ACR criteria. Nonetheless, over time most patients with SLE do accrue sufficient physical and/or laboratory signs to meet 4 or more classification criteria. A patient with nonspecific symptoms who does not meet 4 classification criteria, such as a patient with a positive ANA test, arthralgias, and fatigue, is best diagnosed as having undifferentiated connective tissue disease.

Laboratory Testing
Testing for ANA is often mistakenly employed as a method of screening for SLE. Although detection of ANA has a high sensitivity, with 98% of SLE patients having a positive test, it has a poor specificity. ANA can be detected in approximately 10% to 15% of normal young women. In addition, the ANA titer in SLE patients often is not high (ie, 640 or above). Localized autoimmune disorders (ie, thyroid disease) or systemic autoimmune diseases (eg, undifferentiated connective tissue disease, rheumatoid arthritis, systemic sclerosis, and myositis) are also associated with ANA and other more specific autoantibodies. Antibodies to double-stranded DNA and to Sm are more specific for the diagnosis of SLE. Other antibodies, such as those to ribonucleoprotein (RNP), Ro, and La, and low complement levels (C3 and C4) are not
specific for SLE but are strongly suggestive of connective tissue disease.

Routine laboratory testing is most essential for detecting organ involvement in SLE. A complete blood count with differential will alert the physician to the presence of anemia, leukopenia, lymphopenia, and thrombocytopenia. If anemia is found, a reticulocyte count, haptoglobin count, and direct Coomb's test will determine whether a hemolytic anemia is present. The erythrocyte sedimentation rate (ESR) may be elevated in patients with SLE, but the ESR is not specific for SLE and does not reflect disease activity. Urinalysis with microscopic examination will detect proteinuria, hematuria, or red blood cell casts due to lupus nephritis. Detection of antiphospholipid antibody (positive test for the lupus anticoagulant or antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM antiphospholipid antibodies, 2) a positive test result for lupus anticoagulant, or 3) a false-positive serologic test for syphilis) is a classification criterion for SLE. Antiphospholipid antibodies are markers for hypercoagulability; SLE patients who have these antiphospholipid antibodies are at greater risk for later thrombosis and/or pregnancy loss, especially if the antibodies persist at a high titer. Women who have a medium-to-high titer of antiphospholipid or the lupus anticoagulant should not be exposed to additional risk for thrombosis and therefore should avoid oral contraceptives or hormone replacement therapy.

**Diagnosis**

The case patient has photosensitivity, malar rash, probable oral ulcers, discoid lesions (in the ears), and polyarthritis and thus meets at least 4 of the classification criteria for SLE. The physician makes a diagnosis of SLE.

- What is the epidemiology of SLE?
- What factors are associated with onset or flares of disease?

Like many other autoimmune diseases, SLE shows a female predominance. In addition, a landmark 1974 epidemiologic study confirmed that SLE is more common in African American women than in white women [4]. Most patients are diagnosed after puberty, usually in their 20s or 30s. The Nurse's Health Study suggested that premenopausal women...
exposed to oral contraceptives [5] and postmenopausal women exposed to hormone replacement therapy [6] were more likely to develop SLE. However, exposure to hormone replacement therapy after the diagnosis of SLE has not been associated with lupus flares in case-controlled studies [7].

SLE has a polygenic predisposition. Some HLA-DR and DQ alleles influence the lupus autoantibodies produced. Null complement alleles, which affect immune complex clearance, predispose to lupus as well [8]. Fc-receptor alleles, also involved in immune complex clearance, have been associated with lupus nephritis [9]. Novel research on apoptosis (programmed cell death) has shown that the proteins that SLE patients recognize as foreign are exposed on nuclear blebs [10], suggesting that genes that control apoptosis will be important in SLE. In fact, in murine models, mutations in fas, an essential element in apoptosis, predispose to SLE [11].

The onset of SLE and flares of SLE in patients with established disease are influenced by environmental triggers. The classic example is ultraviolet (UV) light. UV-B and to a lesser extent UV-A are associated with flares of photosensitive rashes and sometimes systemic disease. It is now understood that UV-B leads to apoptosis in keratinocytes, with exposure of Ro protein on nuclear blebs and the potential for anti-Ro/Ro binding [10].

- What therapies are recommended for SLE?
- What issues must be considered when monitoring a patient with SLE?

### Therapy for Mild-to-Moderate SLE

Therapy for cutaneous lupus includes avoiding sun exposure, wearing protective clothing, and using sunblocks that protect against both UV-B and UV-A. Topical corticosteroids play a limited role in cutaneous lupus. Fluorinated compounds should not be used on the face because they may cause atrophy. The mainstay of treatment is antimalarial therapy, usually with hydroxychloroquine. The benefit of hydroxychloroquine has been confirmed in several case-controlled studies and in a prospective randomized withdrawal study [12–15] (Table 2). The risk of retinopathy from hydroxychloroquine is very low [16], but routine ophthalmologic screening is still recommended, usually every 6 months. Additional therapeutic agents for cutaneous lupus include dapsone, retinoids, and corticosteroid-sparing drugs such as methotrexate and mycophenolate mofetil. Thalidomide is used to treat discoid lupus in other countries, but its toxicity (teratogenicity and neuropathy) limits its acceptance in the United States.

Therapy for musculoskeletal lupus includes NSAIDs and hydroxychloroquine. Because of the long-term toxicity of corticosteroids, corticosteroid-sparing drugs such as methotrexate are usually added if the patient requires more than physiologic doses of corticosteroid (ie, prednisone 7.5 mg) chronically.

Acute bouts of pleurisy or pericarditis may require a bolus of high-dose corticosteroids, especially if effusion is present. This can be done effectively by giving intravenous methylprednisolone 1000 mg over 90 minutes daily for 3 days. The maintenance dose of prednisone can then be minimized. NSAIDs are also helpful for controlling chronic serositis.

### Therapy for Major SLE

When major SLE is suspected, consultation with a rheumatologist or other appropriate specialist (eg, nephrologist or hematologist) is needed to confirm the diagnosis and to decide upon treatment options. Diffuse proliferative glomerulonephritis is the most aggressive form of lupus nephritis. Treatment is usually monthly intravenous cyclophosphamide (500 to 1000 mg/m² of body surface area), based on clinical trials showing better outcome with cyclophosphamide than with corticosteroids [17,18]. Renal biopsy is necessary to differentiate proliferative glomerulonephritis from other forms of nephritis, such as mesangial, focal proliferative, and membranous, which may often be controlled with corticosteroids and immunosuppressive drugs (eg, azathioprine and mycophenolate mofetil).

Acute presentation of neurologic lupus, including encephalopathy, stroke, coma, and seizures, should prompt a neurologic consultation and hospitalization of the patient because of the complexity of the differential diagnosis. Neurologic signs in an SLE patient could represent active SLE but might also be clues to infection, hypercoagulability from antiphospholipid antibodies, atherosclerotic events, or complications of hypertension.

### Monitoring Guidelines

All patients with SLE should be monitored for active SLE, even if their disease is apparently inactive, in order to detect signs of...

### Table 2. Controlled Trials of Antimalarials for Treatment of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothfield [12]</td>
<td>Retrospective withdrawal</td>
<td>Decreased flares</td>
</tr>
<tr>
<td>CHSG [13]</td>
<td>Randomized double-blind placebo-controlled withdrawal</td>
<td>Decreased time to flare</td>
</tr>
<tr>
<td>Ruzicka [14]</td>
<td>8-week randomized double-blind</td>
<td>Equal to acitretin</td>
</tr>
<tr>
<td>Levy [15]</td>
<td>Randomized controlled</td>
<td>Decreased flares</td>
</tr>
</tbody>
</table>

CHSG = Canadian Hydroxychloroquine Study Group.
silent organ involvement. Such monitoring should include a complete blood count and urinalysis and a physical examination that includes examination of the skin, chest, heart, and joints at a minimum. Evaluations to monitor for active disease are usually done on a quarterly basis in stable patients.

SLE patients are at greater risk for hypertension, especially those with renal disease. Hypertension should be aggressively treated. A strong case can be made for using angiotensin-converting enzyme (ACE) inhibitors, given their favorable effect on sparing renal sclerosis in other diseases, such as diabetes mellitus.

In addition to causing weight gain and Cushingoid habitus, corticosteroids can cause permanent organ damage. Therefore, it is important to monitor for steroid toxicity. Patients on corticosteroids should have yearly ophthalmologic examinations to detect glaucoma and cataracts, and those maintained on corticosteroids should have screening bone mineral density scans, with follow-up every 2 years for patients with abnormal findings.

Patients with SLE should be monitored for accelerated atherosclerosis. In some centers, 35% of SLE patients have asymptomatic atherosclerosis by carotid duplex scan. Patients with SLE for a duration greater than 5 years should be considered candidates for such screening studies. Hyperlipidemia should be treated aggressively in SLE, given the high morbidity and mortality from atherosclerosis [19].

**Initiation of Treatment**

The rheumatologist adds hydroxychloroquine to the patient’s current NSAID regimen. After 2 months on hydroxychloroquine, the patient has moderate improvement in her cutaneous lupus and lupus arthritis. However, because she still has more than 30 minutes of morning stiffness, obvious warmth over both knees, and discoid lesions in both ears, prednisone is added at 7.5 mg/day. Within 1 week, the patient reports marked improvement in her skin and joints. She will be seen at least every 3 months to monitor for any additional SLE symptoms or signs.

- **What is the prognosis and expected quality of life?**

**Prognosis and Quality of Life**

As mentioned, survival in SLE patients has improved over the past 4 decades. More than half of patients with SLE survive with chronic damage in one or more organ systems [20]. However, 10-year survival after diagnosis in the Rochester study is only about 80% [1]. Causes of mortality include accelerated atherosclerosis [21], thrombosis from antiphospholipid antibodies, infections [22], and complications of renal failure.

Unfortunately, even with advances in therapy for active SLE, quality of life for persons with this disease remains poor. The major patient complaint is chronic fatigue. Chronic fatigue is commonly associated with the rheumatologic syndrome fibromyalgia, in which there are 11 or more tender points in characteristic locations. It is important to emphasize physical rehabilitation in spite of chronic fatigue so that patient level of functioning does not further decline. In addition, we and others have found a higher than expected prevalence of neurally mediated hypotension in this population. Many patients with SLE require therapy with antidepressants [23].

Author’s address: 1830 East Monument St., Suite 7500, Baltimore, MD 21218.

**References**

12. Rothfield N. Efficacy of antimalarials in systemic lupus

Copyright 2000 by Turner White Communications Inc., Wayne, PA. All rights reserved.
EVALUATION FORM: Approach to the Management of Systemic Lupus Erythematosus

To receive 1 hour of AMA PRA Category 1 CME credit, read the article named above and mark your responses on this form. You must complete all parts to receive credit. Then return this form using the fax number or address appearing at the bottom of this page. A certificate awarding 1 hour of category 1 CME credit will be sent to you by fax or mail. This CME Evaluation Form must be fax marked or postmarked within 1 year of this JCOM issue date. Please allow up to 4 weeks for your certificate to arrive.

Part 1. Please respond to each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was provided with new information pertinent to my practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I reaffirmed a specific skill or knowledge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This article will help with clinical decision making.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant clinical outcomes are addressed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The case is communicated in a manner that kept my interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The case presentation is realistic and effective.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I could easily interpret the tables and figures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My attitude about this topic changed in some way.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional comments: ______________________________________________________________________________________</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

- see no need to change my practice.
- will seek more information before modifying my practice.
- intend to change the following aspect(s) of my practice: (Briefly describe)

______________________________________________________________________________
______________________________________________________________________________


Signature: __________________________ Date: __________________________

Part 4. Identifying information: Please PRINT legibly or type the following:

Name: __________________________ Fax number __________________________

Address: __________________________ Telephone number __________________________

Social Security number: __________________________ (Required and confidential)

Medical specialty: __________________________

SEND THE COMPLETED CME EVALUATION FORM TO:

BY FAX: 313-577-7554

BY MAIL: Wayne State University Division of CME
5-E-UHC, 4201 St. Antoine, Detroit, MI 48201

Wayne State University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Wayne State University School of Medicine designates this CME activity for a maximum of 1 hour of category 1 credit toward the Physician’s Recognition Award of the American Medical Association. Physicians should claim only those hours of credit actually spent in the educational activity.