Diagnosis of Systemic Lupus Erythematosus

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Systemic lupus erythematosus is a multisystem inflammatory disease that is often difficult to diagnose. Before the diagnosis can be established, four of 11 clinical and laboratory criteria must be met. Antinuclear antibody titer is the primary laboratory test used to diagnose systemic lupus erythematosus. Because of the low prevalence of the disease in primary care populations, the antinuclear antibody titer has a low predictive value in patients without typical clinical symptoms. Therefore, as specified by the American College of Rheumatology, this titer should be obtained only in patients with unexplained involvement of two or more organ systems. Patients with an antinuclear antibody titer of 1:40 and characteristic multiorgan system involvement can be diagnosed with systemic lupus erythematosus without additional testing; however, patients with an antibody titer of 1:40 who fail to meet full clinical criteria should undergo additional testing, including tests for antibody to double-stranded DNA antigen and antibody to Sm nuclear antigen. While an antinuclear antibody titer of less than 1:40 usually rules out systemic lupus erythematosus, patients with persistent, characteristic multisystem involvement may be evaluated for possible antinuclear antibody–negative disease. (Am Fam Physician 2003;68:2179-86. Copyright© 2003 American Academy of Family Physicians.)

Systemic lupus erythematosus is a chronic, recurrent, potentially fatal multisystem inflammatory disorder that can be difficult to diagnose.[1,2] The disease has no single diagnostic marker; instead, it is identified through a combination of clinical and laboratory criteria.[3] Accurate diagnosis of systemic lupus erythematosus is important because treatment can reduce morbidity[4-11] and mortality,[12] particularly from lupus nephritis. This article reviews evidence-based recommendations for the diagnosis of systemic lupus erythematosus by primary care physicians.

See page 2113 for definitions of strength-of-evidence levels.

Methods

We conducted a systematic evidence-based review of the published literature on systemic lupus erythematosus. After searching several evidence-based databases *(Table 1)*, we reviewed the MEDLINE database using the PubMed search engine. Search terms included "lupus *not* discoid *not* review *not* case" and "lupus *and* treatment *and* mortality," with the following limits: 1996 to present, abstract available, human, and English language. One author reviewed qualifying studies for relevance and method.

TABLE 1
Resources Used for an Evidence-Based Review of the Literature on Systemic Lupus Erythematosus

American College of Physicians Journal Club (http://www.acpjc.org)
National Guideline Clearinghouse Database (http://www.guideline.gov)
Agency for Healthcare Research and Quality Database (http://www.ahcpr.gov)
Turning Research into Practice Database (http://www.tripdatabase.com)
Cochrane Database of Systematic Reviews (http://www.cochrane.org)
British National Health Service Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/)

In the United States, systemic lupus erythematosus is reported to be more common in women, particularly black women, than in white men.

When meta-analyses or systematic reviews were identified, they were used instead of the original research articles. For diagnosis, only studies with controls were included. Bibliographies from the articles were used to identify additional articles that we thought were important.

Results

PREVALENCE

Only one population-based screening study[13] of systemic lupus erythematosus was identified. This study reported a prevalence of 200 cases per 100,000 women (18 to 65 years of age) in England. One review[14] estimated the overall U.S. prevalence of definite systemic lupus erythematosus plus incomplete systemic lupus erythematosus (disease meeting only some diagnostic requirements for systemic lupus erythematosus) to be 40 to 50 cases per 100,000 persons.

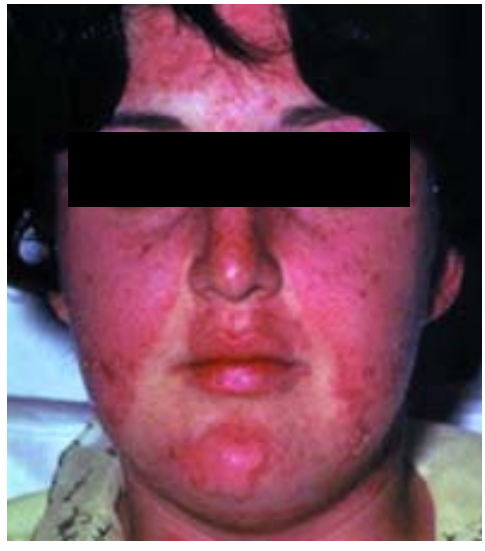

FIGURE 1. Malar rash, the most common cutaneous manifestation of systemic lupus erythematosus.

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No screening studies on the prevalence of systemic lupus erythematosus in children were identified. However, a review article[15] reported that systemic lupus erythematosus is estimated to affect 5,000 to 10,000 U.S. children.

In the United States, systemic lupus erythematosus is reported to be more common in women, particularly black women, than in white men.[14,16] One U.S. retrospective study[16] of medical records found that the disease is diagnosed 23 times more often in black women than in white men. The prevalence of the disease is also higher in Hispanic and Asian Americans.[16] In addition, a familial predisposition to systemic lupus erythematosus has been identified.[17-19]

CLINICAL MANIFESTATIONS

Systemic lupus erythematosus most often manifests as a mixture of constitutional symptoms, with skin *(Figure 1)*, musculoskeletal, and hematologic (mild) involvement *(Table 2)*.[2,20,21] However, some patients present with predominantly hematologic, renal, or neuropsychiatric manifestations.[20]

Patients with systemic lupus erythematosus appear to be at high risk for coronary artery disease.[22-24] Infections, especially of the respiratory and urinary systems, also are common in patients with the disease and are difficult to distinguish from flares of lupus activity.[1,20]

The clinical manifestations of systemic lupus erythematosus are fundamentally the same in children and adults.[15] In two descriptive studies[25,26] of children with the disease, the most frequent manifestations were fever, rash, arthritis, alopecia, and renal involvement. Compared with adults, children have a higher incidence of malar rash, anemia, leukocytopenia,[27] and severe manifestations such as neurologic or renal involvement.[28]

MORBIDITY AND MORTALITY

Organ damage in systemic lupus erythematosus progresses over time.[29] A cohort study[30] found that within seven years of diagnosis, 61 percent of patients developed clinically detectable organ damage, with neuropsychiatric (20.5 percent), musculoskeletal (18.5 percent), and renal (15.5 percent) organ systems most commonly affected.

A cohort study found that within seven years of diagnosis, 20.5 percent of patients with systemic lupus erythematosus have neuropsychiatric damage, 18.5 percent have musculoskeletal damage, and 15.5 percent have renal damage.

Remission of systemic lupus erythematosus is not uncommon but often is punctuated by flares.[31] In a six-year prospective cohort study,[23] disease flares occurred at a rate of 0.2 per year per patient.

Infections and diseases of the cardiovascular, renal, pulmonary, and central nervous systems are the most frequent causes of death in patients with systemic lupus erythematosus.[8,23,32-37] Since the 1950s, the five-year survival rate for patients with systemic lupus erythematosus has increased from 50 percent to a range of 91 to 97 percent.[8,23,32-34,38,39] It is not known how much of this increase in survival is due to improved management versus diagnosis of earlier and milder disease. Higher mortality rates are associated with seizures, lupus nephritis, and azotemia.[36,37,40]

Mortality rates for systemic lupus erythematosus are particularly high in children. In a retrospective study[26] of Brazilian children, overall mortality during 16 years of follow-up was 24 percent. Death occurred because of infection (58 percent), central nervous system disease (36 percent), and renal disease (7 percent). When disease onset was before the age

TABLE 2
Clinical Features of Systemic Lupus Erythematosus

Affected organ system	*Percentage of patients*[20]	*Signs and symptoms*
Constitutional	50 to 100	Fatigue, fever (in the absence of infection), weight loss
Skin	73	Butterfly rash, photosensitivity rash, mucous membrane lesion, alopecia, Raynaud's phenomenon, purpura, urticaria, vasculitis
Musculoskeletal	62 to 67	Arthritis, arthralgia, myositis
Renal	16 to 38	Hematuria, proteinuria, cellular casts, nephrotic syndrome
Hematologic	36[21]	Anemia, thrombocytopenia, leukopenia
Reticuloendothelial	7 to 23	Lymphadenopathy, splenomegaly, hepatomegaly
Neuropsychiatric	12 to 21	Psychosis, seizures, organic brain syndrome, transverse myelitis, cranial neuropathies, peripheral neuropathies
Gastrointestinal	18	Nausea, vomiting, abdominal pain
Cardiac	15	Pericarditis, endocarditis, myocarditis
Pulmonary	2 to 12	Pleurisy, pulmonary hypertension, pulmonary parenchymal disease

Adapted with permission from Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 1999;42:1785-96, with additional information from references 20 and 21.

of 15 years, renal involvement and hypertension predicted mortality.

Diagnosis

The diagnosis of systemic lupus erythematosus is based on clinical and laboratory criteria. The criteria set developed by the American College of Rheumatology (ACR) is most widely used *(Table 3)*.[41,42] An algorithm for the diagnosis of the disease is provided in *Figure 2*.[2,20,21,41,42]

In one study[41] that used patients with connective tissue diseases as the control group, the revised ACR diagnostic criteria for systemic lupus erythematosus were found to have an overall sensitivity of 96 percent and a speci-

TABLE 3
American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

The diagnosis of systemic lupus erythematosus requires the presence of four or more of the following 11 criteria, serially or simultaneously, during any period of observation.

1. Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash: erythematous, raised patches with adherent keratotic scaling and follicular plugging; possibly atrophic scarring in older lesions
3. Photosensitivity: skin rash as a result of unusual reaction to sunlight, as determined by patient history or physician observation
4. Oral ulcers: oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis: nonerosive arthritis involving two or more peripheral joints, characterized by swelling, tenderness, or effusion
6. Serositis: pleuritis, by convincing history of pleuritic pain, rub heard by physician, or evidence of pleural effusion; or pericarditis documented by electrocardiography, rub heard by physician, or evidence of pericardial effusion
7. Renal disorder: persistent proteinuria, > 500 mg per 24 hours (0.5 g per day) or > 3+ if quantitation is not performed; or cellular casts (may be red blood cell, hemoglobin, granular, tubular, or mixed cellular casts)
8. Neurologic disorder: seizures or psychosis occurring in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder: hemolytic anemia with reticulocytosis; or leukopenia, < 4,000 per mm^3 (4.0×10^9 per L) on two or more occasions; or lymphopenia, < 1,500 per mm^3 (1.5×10^9 per L) on two or more occasions; or thrombocytopenia, < 100×10^3 per mm^3 (100×10^9 per L) in the absence of offending drugs
10. Immunologic disorder: antibody to double-stranded DNA antigen (anti-dsDNA) in abnormal titer; or presence of antibody to Sm nuclear antigen (anti-Sm); or positive finding of antiphospholipid antibody based on an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false-positive serologic test for syphilis that is known to be positive for at least 6 months and is confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibodies: an abnormal antinuclear antibody titer by immunofluorescence or equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus

Adapted with permission from Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1274, and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [Letter]. Arthritis Rheum 1997;40:1725.

ficity of 96 percent. Other studies[21,32,43] have reported sensitivities ranging from 78 to 96 percent and specificities ranging from 89 to 100 percent. The ACR criteria may be less accurate in patients with mild disease.[21]

Elevation of the antinuclear antibody (ANA) titer to 1:40 or higher is the most sensitive of the ACR diagnostic criteria. More than 99 percent of patients with systemic lupus erythematosus have an elevated ANA titer at some point,[21,41] although a significant proportion of patients may have a negative ANA titer early in the disease.[2] However, the ANA test is not specific for systemic lupus erythematosus. A study[41] involving 15 international laboratories found that ANA tests in the general population were positive in 32 percent of persons at a 1:40 dilution and in 5 percent of persons at a 1:160 dilution. Rates of positive ANA tests were not affected by age up to 60 years (the upper age limit of the study).[41]

In the absence of systemic lupus erythematosus, the most common reason for a posi-

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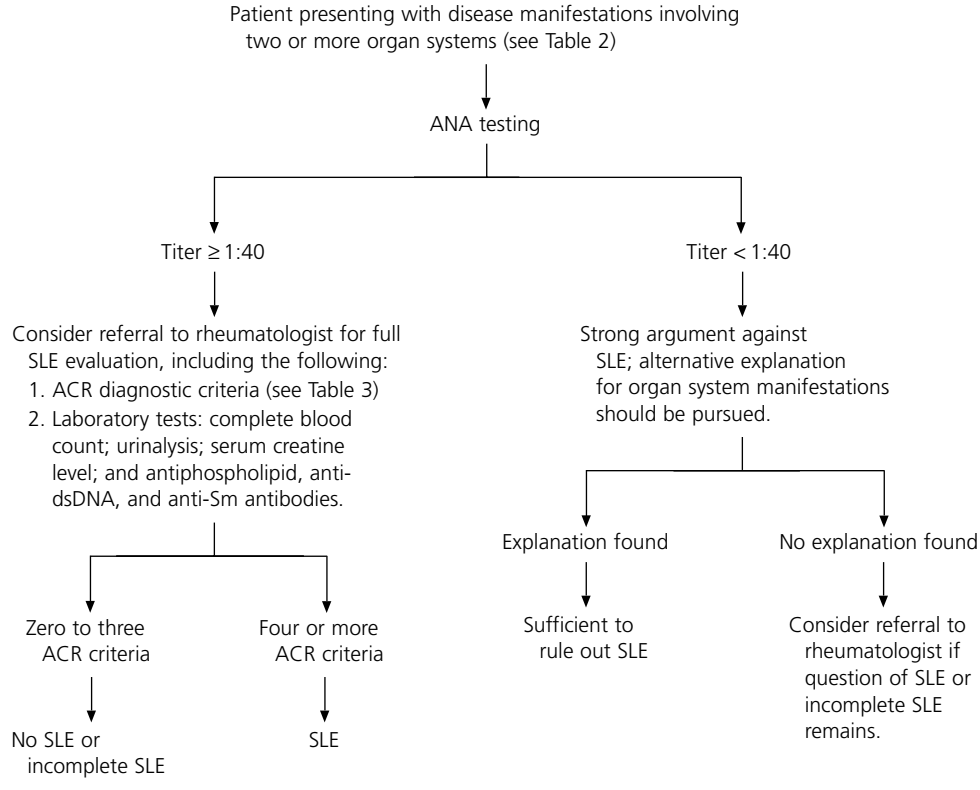

FIGURE 2. An algorithm for the diagnosis of systemic lupus erythematosus (SLE). (ANA = antinuclear antibody; ACR = American College of Rheumatology; anti-dsDNA = antibody to double-stranded DNA antigen; anti-Sm = antibody to Sm nuclear antigen)

Information from references 2, 20, 21, 41, and 42.

The American College of Rheumatology recommends antinuclear antibody testing in patients with two or more unexplained signs or symptoms of systemic lupus erythematosus.

tive ANA test is the presence of another connective tissue disease. Diseases that often are associated with a positive ANA test include Sjögren's syndrome (68 percent of affected patients), scleroderma (40 to 75 percent), rheumatoid arthritis (25 to 50 percent), and juvenile rheumatoid arthritis (16 percent).[20] An ANA test also can be positive in patients with fibromyalgia. In patients with diseases other than systemic lupus erythematosus, ANA titers usually are lower, and the immunofluorescent pattern is different.[20]

Rates of positive ANA tests are affected by the prevalence of systemic lupus erythematosus in the population. Specifically, false-positive rates will be higher in populations with a low prevalence of the disease, such as primary care patients. Because of the high false-positive rates at 1:40 dilution, ANA titers should be obtained only in patients who meet specific clinical criteria (discussed in the clinical recommendations section of this article). When ANA titers are measured, laboratories should report ANA levels at both 1:40 and 1:160 dilutions and should supply information on the percentage of normal persons who are positive at each dilution.[41]

Interpretation of ANA titers is similar in children. An ANA titer of less than 1:40 is useful for ruling out systemic lupus erythematosus (sensitivity of 98 percent). However, an ANA titer of 1:40 or higher has a positive predictive value of only 10 percent because of the common occurrence of high ANA titers in children.[44]

Clinical Recommendations

The ACR recommends ANA testing in patients who have two or more unexplained signs or symptoms listed in *Table 2*.[2,20,21] [Reference 2—Evidence level C, consensus/expert guidelines] Because of the high rate of false-positive ANA titers, testing for systemic lupus erythematosus with an ANA titer or other autoantibody test is not indicated in patients with isolated myalgias or arthralgias in the absence of these specific clinical signs.[45] Under most circumstances, a persistently negative ANA titer (less than 1:40) can be assumed to rule out systemic lupus erythematosus.[41]

A normal-range ANA titer in the context of organ system involvement that suggests systemic lupus erythematosus should prompt a work-up for alternative diagnoses. If no other cause is identified, the diagnosis of ANA-negative systemic lupus erythematosus and consultation with a rheumatologist should be considered. If patients with a normal ANA titer develop new clinical features that are consistent with systemic lupus erythematosus, ANA testing should be repeated.[46] [Evidence level C, consensus/expert guidelines]

According to a guideline from the College of American Pathologists (CAP), no further laboratory tests are necessary in patients who meet diagnostic criteria for systemic lupus

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erythematosus and also have a positive ANA test result.[46]

Testing for antibody to double-stranded DNA antigen (anti-dsDNA) and antibody to Sm nuclear antigen (anti-Sm) may be helpful in patients who have a positive ANA test but do not meet full criteria for the diagnosis of systemic lupus erythematosus. Anti-dsDNA and anti-Sm, particularly in high titers, have high specificity for systemic lupus erythematosus, although their sensitivity is low. Therefore, a positive result helps to establish the diagnosis of the disease, but a negative result does not rule it out.[46] The CAP guideline recommends against testing for other autoantibodies in ANA-positive patients, because there is little evidence that these tests are of benefit.[46]

The ACR recommends that primary care physicians consider a rheumatology referral for patients with characteristic signs and symptoms of systemic lupus erythematosus *(Table 2)*[2,20,21] and a positive ANA test, particularly if these patients have more than mild or stable disease.[2] [Reference 2—Evidence level C, consensus/expert guidelines]

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