Assessment of systemic lupus erythematosus

G.K.W. Lam, M. Petri

Department of Medicine, Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Gordon K.W. Lam, MD; Michelle Petri, MD, MPH.

Please address correspondence to: Michelle Petri, MD, MPH, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore MD 21205, USA.
E-mail: mpetri@jhmi.edu

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ABSTRACT

Systemic lupus erythematosus (SLE) is the archetypal autoimmune disease given its complex clinical and molecular manifestations. Like the other rheumatic diseases, appropriate management is critically dependent upon the proper assessment of disease activity, organ damage, and quality of life. Here, we describe the components of the comprehensive assessment of SLE, including accurate physical and laboratory diagnosis, monitoring of disease activity, recording of accumulated organ morbidity, and integration of these with the patient's own perceptions of health status and quality of life. In doing so, we will review the most appropriate laboratory tests and indices currently used in standard clinical care and in clinical research.

Introduction

SLE is an idiopathic connective tissue disease, the spectrum of which covers a wide array of clinical and laboratory manifestations. While the etiology of SLE is thought to be multifactorial, the disease is characterized by the production of autoantibodies which leads to immune complex deposition, inflammation, and eventually, permanent organ damage. SLE is considered to be one of the most common autoimmune disorders of women of childbearing age, having an estimated prevalence of 14.6 to 50.8 per 100,000 persons in this category in the United States (1-3). There is a female:male ratio of approximately 6-10:1, with a peak incidence between the ages of 15 and 40. However, SLE can affect all age groups, from infants to geriatric patients.

Accurate clinical assessment of SLE is desirable because this disease has a complex phenotype, a variable disease course, and cumulative morbidity over time, as new organ system involvement may be seen over time in many patients even 5 to 10 years after diagnosis (4). Many studies now show 5-year survival rates exceeding 90% (5-7). However, the survival of SLE patients has not improved since the 1980s, with atherosclerosis remaining the major cause of death. Hence, measures for diagnosing SLE, monitoring disease activity, assessing tissue damage, and recognizing effects on individual patients are all important and necessary.

Assessment of SLE can be divided into 4 components: 1) Accurate diagnosis; 2) Monitoring disease activity; 3) Assessment of accumulated damage morbidity; and 4) Determining the patient's health status throughout his or her course.

Diagnosis of SLE

Clinical manifestations

The complex and protean nature of SLE demands a meticulously derived history, thorough physical examination, and appropriate laboratory analysis. Constitutional symptoms such as malaise, fatigue, fever, and unintentional weight loss are common presenting symptoms of SLE. These symptoms are not specific to just SLE, and diligence should be given to discerning other etiologies such as fibromyalgia, depression, infection, malignancy, endocrinopathy, or other connective tissue diseases on initial presentation. In addition, environmental triggers such as exposure to ultraviolet radiation, infection, or the use of certain medications (such as Echinacea, sulfonamide antibiotics, minocycline and anti-TNF biologics) should be identified, if possible.

SLE can affect any organ system and can present in differing combinations. The most frequent manifestations include: arthritis (64-91%), skin lesions (55-86%), renal involvement (28-73%), Raynaud's phenomenon (24-61%), central nervous system involvement (11-49%), gastrointestinal symptoms (39%), pleurisy (27-36%), pericarditis (12-20%), lymphadenopathy (10-30%), nephrotic syndrome (13-14%), lung involvement (7-14%), thrombophlebitis (5-14%), myositis (4-9%), and myocarditis (2-3%) (8).

Arthritis and arthralgias are the most common presenting manifestations of SLE. Any joint may be affected, but the small joints of the hands and wrists, and occasionally knees are typically involved. SLE arthralgias/arthritis are usually symmetric and polyarticular. Inflammation may be migratory or persistent. In contrast to rheumatoid arthritis, arthritic changes are usually not erosive or destructive; therefore, radiographic findings in SLE patient are usually minimal. If joint subluxations occur, they can be reducible (the so-called Jaccoud's arthropathy) (9).

Skin manifestations in SLE are also widely recognized. They may be classified into three types based on their appearance and duration: acute, subacute, and chronic. The malar rash is the most identifiable acute lesion, marked by erythema and elevation in a "butterfly" distribution that spares the nasolabial folds. On history, exposure to ultraviolet light is one of its precipitating factors. Other types of acute cutaneous lupus include photosensitive maculopapular rashes.

Subacute cutaneous lupus erythematosus is a distinct lesion that begins as erythematous papules or plaques and may evolve into papulosquamous lesions resembling psoriasis or annular lesions resembling erythema annulare centrifugum. Chronic cutaneous lupus usually presents as discoid lesions, which are erythematous papules or plaques that progress to thick, hyperkeratotic lesions with scarring and central atrophy. On the scalp, these lesions may lead to permanent alopecia. Finally, a number of lesions not specific to SLE are also commonly found, including mucocutaneous ulcerations involving the oral, nasal, and genital mucosa, generalized alopecia, livedo reticularis (which is also associated with the antiphospholipid antibody syndrome), splinter hemorrhages, palpable purpura, panniculitis, urticaria, bullous lesions, and Raynaud's phenomenon.

The majority of SLE patients are afflicted with renal disease. In our center, 50% of Caucasian patients and 75% of African-American patients eventually have lupus nephritis. The diagnosis of SLE nephritis requires proteinuria (the American College of Rheumatology classification criteria define this as 0.5 g per 24 hours or a dipstick score of > 3+) or the presence of casts on microscopic analysis of spun urine (including red blood cells, heme, granular, tubular, or mixed casts). Renal disease may also be manifested by an increased serum creatinine level, or by the presence of hematuria, pyuria, or both in the absence of infection or menses. Renal biopsies may be helpful in determining the degree of renal involvement, and therefore in delineating treatment decisions and prognosis in certain clinical scenarios. The World Health Organization (WHO) has classified lupus nephritis based on the presence of light, immunofluorescence, and electron microscopy characteristics (Table I) (10). Class IV (Diffuse proliferative glomerulonephritis), V (Membranous glomerulonephritis), and VI (Advanced sclerosing glomerulonephritis) are associated with poor prognosis and decreased survivial. Conversely, the presence of active lesions would support the use of aggressive anti-inflammatory and immunosuppressive therapies. The WHO classification scheme has now been supplanted by the ISN classification (11).

The incidence of neurologic and psychiatric manifestations of SLE has been difficult to estimate as many of the symptoms are non-specific (e.g. headache, depression, anxiety), and some, such as depression, anxiety, and psychosis, may be caused by or worsened by therapies including corticosteroids. In 1994, the American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature proposed a standardized nomenclature for the neuropsychiatric syndromes of SLE (12). Neurologic features of SLE span the central, peripheral, and autonomic nervous systems. Specific entities include seizures (grand mal, petit mal, focal, temporal lobe), stroke, movement disorders (chorea), intractable headaches, transverse myelitis, cranial neuropathy (most commonly retinopathy secondary to vasculitis), and peripheral neuropathy. Psychiatric features include cognitive dysfunction, psychosis, psychoneurosis, and organic brain syndrome. Neuropsychiatric lupus is primarily a clinical diagnosis, but it is essential to exclude infection, hypertensive emergency, and uremia. In this regard, cerebrospinal fluid and a magnetic resonance image of the brain may be useful in the evaluation of patients with neuropsychiatric symptoms.

Gastrointestinal involvement in SLE ranges from relatively mild problems, such as dyspepsia, to life-threatening emergencies such as mesenteric vasculitis. In the latter instance, patients may complain of post-prandial abdominal pain and bleeding per rectum. Abdominal CT scan with contrast, colonoscopy and arteriography may reveal evidence of inflammation, perforations, or vasculitis. Other gastrointestinal symptoms, such as esophageal dysmotility, inflammatory bowel disease, pancreatitis, liver disease, and peritonitis (see below) are less common.

Serositis is commonly reported in SLE, typically as pleurisy, pericarditis, and peritonitis. Clinical assessment of pleural manifestations includes a history of pleuritic chest pain, rubs on auscultation of the lungs, and areas of decreased breath sounds or dullness to percussion if pleural effusions are present. Pleural effusions are frequently bilateral, and if large, a thoracocentesis should be performed. The fluid is usually exudative by Light's criteria (13) with a normal glucose concentration and an inflammatory infiltrate. The presence of anti-nuclear antibodies (ANA) in the pleural fluid may be sensitive for SLE, but it is not a necessary component for diagnosis (14).

Pleurisy is more frequent than pericarditis, as pericarditis can be clinically silent and pericardial effusions are difficult to detect on physical examination. If present, a pericardial rub and classic electrocardiogram signs (diffuse STsegment elevations, PR depression, and low voltages) are diagnostic of pericarditis. Echocardiography may be useful to detect pericardial effusions. Cardiac tamponade is rare, and pericardiocentesis is rarely indicated. Connective tissue diseases, including SLE, accounted for 12% of cases of pericardial effusions in a tertiary care facility (15).

Table I. World Health Organization (WHO) classification of lupus nephritis.

Class	Histology	Clinical presentation	Prognosis
I. Normal	Normal	No abnormalities	Excellent
II. Mesangial	Mesangial hypertrophy Mesangial immune complex deposits complex depositis	No abnormalities in 25% Minimal proteinuria	Good
III. Focal proliferative	Mesangial and endothelial proliferation Immune deposition along capillaries < 50% glomeruli involved	Mild proteinuria (500-3500 mg/24h) Nephrotic syndrome in 20% Mild hematuria	Moderate
IV. Diffuse proliferative	Subendothelial immune deposits Cell proliferation Crescents Hematoxylin bodies Hematoxylin bodies > 50% glomeruli involved	Moderate to heavy proteinuria Hematuria with RBC casts Mild to severe renal insufficiency Hypertension present	Poor
V. Membranous	Subepithelial granular immune deposits	Nephrotic range proteinuria Microscopic hematuria Hypertension	Moderate
VI. Sclerosing	Focal segmental and global glomerular sclerosis Fibrous crescents Vascular sclerosis	Severe renal insufficiency End stage renal disease	Poor

Adapted from Goldbus J, McClune WJ: Lupus nephritis. Classification, prognosis, immunopathogenesis and treatment. *Rheum Dis Clin North Am* 1994; 20: 213-42.

In addition to pleurisy, other pulmonary manifestations of SLE include lupus pneumonitis, pulmonary hemorrhage, pulmonary embolism, and pulmonary hypertension. Acute lupus pneumonitis mimics pneumonia with symptoms of fever, cough, and shortness of breath. Bronchoalveolar lavage is indicated when infection versus inflammation needs to be ascertained. Chronic forms of lupus pneumonitis are marked by dry cough, dyspnea on exertion, crackles on auscultation of the lungs, and interstitial infiltrates on imaging.

Pulmonary hemorrhage, marked by hemoptysis and confirmed by bronchoscopy, is thought to result from vasculitis of the pulmonary vessels. While uncommon, it can be a medical emergency. Diffuse alveolar hemorrhage is associated with acute lupus pneumonitis and has a mortality rate of 50%.

Pulmonary embolism may be underrecognized in SLE patients, especially if antiphospholipid antibodies (anticardiolipin, lupus anticoagulant, or anti-beta 2 glycoprotein 1) are present, which predispose to thromboembolic disease. Chronic pulmonary emboli may be a secondary cause of pulmonary hypertension, although a primary, idiopathic form is seen in SLE as well. The prevalence of pulmonary hypertension by echocardiography has been estimated at 14% (16). Pulmonary function tests indicate a restrictive pattern and a reduced carbon dioxide diffusing capacity. On physical examination, hypoxia, dyspnea, and Raynaud's phenomenon are often present.

Cardiac symptoms in SLE may present insidiously. In addition to pericarditis, myocarditis, endocarditis, and coronary artery disease have been identified. Myocardial disease may be subtle, but should be considered in the differential diagnosis of any patient with arrhythmias, tachycardia, and cardiomegaly. Endomyocardial biopsy is helpful (17) and could guide treatment towards the use of corticosteroids. Endocarditis is classically associated with non-bacterial verrucous vegetations (Libman-Sacks disease) on the mitral and tricuspid valves. Advanced disease requires valvular replacement but carries with it significant risks. More commonly, atherosclerosis and coronary artery disease are found in SLE patients. Likely exacerbated by the use of corticosteroids during various stages of their disease, cardiovascular disease is acknowledged as the main cause of death later in the course of SLE, resulting in a bimodal mortality curve (18). The risk of myocardial infarction is increased 50-fold in young women with SLE (19). Even after adjustment for traditional cardiovascular risk factors, the risk of myocardial infarction is still increased 8-fold (20).

Laboratory findings

While the hallmark of SLE is the presence of antinuclear antibodies, a number of laboratory abnormalities characterize lupus.

Serologically, the production of various autoantibodies is the immunopathologic basis of disease. A positive ANA is perhaps the most important finding to establish initially, as this implicates autoimmunity. However, a positive ANA is non-specific and can be found in 5-20% of the normal population (21, 22). Anti-Sm antibodies are also diagnostic of SLE, seen with a frequency of 30-40%. Conversely, ANA-negative lupus, while extremely rare, may exist. Antibodies to double-stranded DNA (dsDNA) are found in 40-60% of SLE patients. They are associated with renal involvement but do not correlate well with disease activity. In fact, in a prospective study, anti-dsDNA levels fell on the day of a flare, possibly owing to

deposition of antibodies in the tissues at the peak of clinical disease (23). Therefore, while patients with elevated levels of anti-dsDNA over many years of disease have a poorer prognosis compared to those who do not, acute changes in the titers of anti-dsDNA do not predict disease flare at the next clinic visit.

Antiphospholipid antibodies may also be found in lupus (50%) and can cause venous and arterial thromboses, as well as recurrent fetal loss. Assessment is by the detection of antibodies to cardiolipin or to beta-2 glycoprotein 1, or by the presence of a lupus anticoagulant, which is marked by prolonged clotting times that are not corrected by mixing studies *in vitro*. Anti-SSA/Ro and anti-SSB/La are associated with secondary Sjögren's syndrome, subacute cutaneous lupus erythematosus, neonatal lupus, and photosensitivity.

Autoantibodies lead to the formation of immune complexes, which activate and consume complement. Hence, measuring levels of C3, C4, or total hemolytic complement CH50 may be helpful in the diagnosis of lupus (24), as well as in the routine monitoring of SLE patients. However, hypocomplementemia is not specific to SLE and can be found in any disease in which there is a large antigen-antibody load. Prospective studies have not found changes in C3 or C4 to predict overall disease activity, but they were reduced with hematologic and renal flares on the same day the flare occurred (25).

Hematologic abnormalities are common findings in SLE. Anemia may reflect chronic inflammation, renal disease, iron deficiency or gastrointestinal loss. In addition, an autoimmune, hemolytic anemia caused by autoantibodies against red blood cell antigens (Coombs positivity) can occur (26). An appropriate reticulocytosis excludes marrow suppression as the underlying etiology of the anemia.

Leukopenias and thrombocytopenias are common in SLE patients. They are thought to be secondary to antibodies directed against cell surface antigens. As with the other cytopenias, infection, malignancy, and adverse drug effects need to be ruled out.

Common laboratory tests obtained on initial evaluation are listed in Table II.

ACR classification criteria

Because of the vast clinical and laboratory manifestations of SLE, Cohen *et al.* (27) published the first classification criteria for SLE in 1971. It was subsequently revised in 1982 by Tan *et al*. (28) and adopted by the ACR. Its most recent modification in 1997 (29) is the current ACR Criteria for the Classification of SLE (Table III). In it, 11 classification criteria are identified that reflect the major clinical manifestations of the disease, including mucocutaneous, articular, serosal, renal, neurologic, hematologic, and immunologic features. The presence of 4 or more of these criteria, either serially or simultaneously and during any interval of observation, identifies a patient as having SLE for research purposes.

Since its publication, the ACR classification criteria have been validated by a number of studies (30-33), and it is now almost universally used in clinical practice and in clinical trials. However, there is general agreement that the classification criteria are not perfect. For example, they over-represent cutaneous manifestations of lupus; they lack sensitivity for the detection of early disease; they do not capture some patients with lupus nephritis and neurologic lupus; hypocomplementemia is absent as a criterion; little crosscultural and ethnic validation has been performed; and the 1997 modifications have not been validated (34). In addition, the original intent of the classification criteria was for clinical research purposes, not necessarily for diagnosis in clinical practice. Because it may take years from the first sign of SLE until the patient manifests 4 criteria, the classification criteria are not valid for incident SLE. As such, efforts are currently underway to revise and update the ACR classification criteria for SLE (34).

Assessing disease activity

Continued disease activity has become generally accepted as part of the natural history of SLE. It is well-known that patients continue to have disease activity 10 years after diagnosis (35) even with appropriate management, often involving new organ systems (4). Three patterns of disease activity have emerged: the flare (or "remitting relapsing pattern"), chronically active disease, or long quiescence (36). These patterns can be discerned using systematic clinical assessments, routine laboratory tests, and standardized measures of disease activity.

Table II. Common laboratory tests obtained on the initial evaluation of SLE.

Complete blood count
Comprehensive metabolic panel
24-hour urine for protein and creatinine
Urinalysis
Erythrocyte sedimentation rate
C-reactive protein
Antinuclear antibody
Anti-double stranded DNAantibody
Anti-Sm (and anti-RNP) antibody
Anti-SSA/Ro antibody
Anti-SSB/La antibody
Anticardiolipin antibodies (IgG, IgM, IgA)
Anti-beta 2 glycoprotein 1 antibodies
Prothrombin time/INR
Partial thromboplastin time
Mixing studies, if indicted
Lupus anticoagulant
Dilute Russel Viper Venom time (a lupus anticoagulant test)
C3, C4, CH50
Thyroid studies
Fasting lipid panel
Homocysteine
Fibrinogen
Coombs' test

Clinical assessment

Although flares of SLE are usually mimetic, the disease itself can evolve over time with the accumulation of tissue injury and with new organ system involvement. Hence, a thorough history, broad review of systems, and complete physical examination should be performed at each clinic visit to assess disease activity. When screening for symptoms, it is important to determine indicators of active lupus, adverse drug effects, complications of disease such as infection or cardiovascular disease, or other comorbidities such as fibromyalgia, depression, cancer or thyroid disease. If a positive finding is elicited, it is then important to further characterize it (How long has it been present? Is it

Table III. American College of Rheumatology (ACR) criteria for the classification of systemic lupus erythematosus.

Criterion	Definition
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; atrophic scarring may occur in older lesions.
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR b) Pericarditis—documented by ECG or rub or evidence of pericardial effusions
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed OR b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures—in the absence of offending drugs or known metabolic derangements OR b) Psychosis—in the absence of offending drugs or known metabolic derangements
9. Hematologic disorder	a) Hemolytic anemia—with reticulocytosis OR b) Leukopenia—less than 4000/mm3 total on two or more occasions OR c) Lymphopenia—less than 1500/mm^3 on two or more occasions OR d) Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) Anti-DNA: antibody to native DNAin abnormal titer OR b) Anti-Sm: presence of antibody to Sm or nuclear antigen OR c) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies; (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome.

For the purpose of identifying patients in clinical studies, a person must have SLE if any of 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
Adapted from Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.

improving, worsening, or stable? Has it happened before? If so, how was it treated? What triggered it?). In doing so, a physician is able to judge the severity of the activity and gain a sense of the degree of treatment that would be appropriate.

Laboratory tests

While the history and physical examination are most important in assessing disease activity, laboratory tests are helpful in organ systems (hematologic, renal) that cannot be assessed clinically. The most useful tests are generally suggested by the history and physical examination, but because flares are typically mimetic, a pattern in each patient often becomes evident clinically and objectively.

Leukopenia is one of the common manifestations of lupus. However, because some immunomodulatory agents (e.g. cyclophosphamide, azathioprine) can cause leukopenia, care must be taken in determining whether it represents SLE versus drug toxicity. Thrombocytopenia may be due to an active lupus flare, to immunosuppressive drugs, or to the antiphospholipid antibody syndrome. However, because platelets are an acute phase reactant, the platelet count can also be elevated during periods of inflammation. The erythrocyte sedimentation rate (ESR) and the C-reactive protein level (CRP) are markers of inflammation, but they do not accurately reflect disease activity. The ESR can be elevated in renal insufficiency (37), hypoalbuminemia, hypergammaglobulinemia, or anemia. The CRP is usually normal or only slightly elevated. If markedly elevated, infection should be considered.

The high prevalence of renal disease in

Table IV. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

Wtd score	Descriptor	Definition.
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug-related causes.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude the presence of uremia and offending drugs.
8	Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or syndrome other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug-related causes.
8	Visual	Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection).
8	Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve.
8	Lupus headache	Severe, persistent headache; may be migranous; unresponsive to narcotics.
8	Cerebrovascular accident	New syndrome. Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages. Vasculitis confirmed by biopsy or angiogram.
4	Arthritis	More than 2 joints with pain and signs of inflammation .
4	Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or a biopsy showing myositis.
4	Casts	Heme, granular, or erythrocyte.
4	Hematuria	More than 5 erythrocytes per high power field. Exclude other causes (stone, infection).
4	Proteinuria	More than 0.5 grams of urinary protein excreted per 24h. New onset or recent increase of > 0.5 g/24h.
4	Pyuria	More than 5 leukocytes per high-power field. Exclude infection.
2	New malar rash	New onset or recurrence of an inflammatory type of rash.
2	Alopecia	New or recurrent. Apatch of abnormal, diffuse hair loss.
2	Mucous membranes	New onset or recurrence of oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by electro- or echocardiography.
2	Low complement	Adecrease in CH50, C3, or C4 level (to less than the lower limit of the laboratory-determined normal range).
2	Increased DNAbinding	More than 25% binding by Farr assay (to >the upper limit of the laboratory-determined normal range, e.g. 25%).
2	Fever	More than 38 ºC after the exclusion of infection.
2	Thrombocytopenia	Fewer than 100,000 platelets
2	Leukopenia	Leukocyte count of < 3000/mm^3 (not due to drugs)

Adapted from Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35: 630-40.

SLE patients warrants routine monitoring of SLE renal activity. Monitoring urinalyses and creatinine provide convenient screens for renal activity. A urine dipstick is a quick screen for proteinuria, hematuria, and signs of infection. Microscopic examination can identify nephritis by the presence of hematuria or casts (see above). More accurate assessments of renal function can be obtained by a 24-hour urine collection for protein and creatinine (38). Recently, the urine protein-to-creatinine ratio has been found to be a reliable measure of proteinuria in lupus nephritis (39) and is less dependent on patient compliance. Lastly, renal biopsy is the most definitive way of assessing activity and damage (i.e., chronicity), in addition to helping with classification (see above). Thus, it can guide therapeutic decisions.

Serologic tests are usually not helpful in predicting disease activity. Hypocomplementemia and rising titers of anti-dsDNAindicate increased immune complex formation and complement activation, but their association with clinical flares is imperfect. As discussed above, neither anti-dsDNA nor low complement levels predicted future flares in prospective studies. On the day of the flare, anti-dsDNAwas most likely to have fallen; C3 and C4 decreased only with renal or hematologic flares (23, 25). Lastly, mucocutaneous flares

Table V. British Isles Lupus Assessment Group (BILAG) Index.
Note: It is implicit in this scoring system that all features scored are thought to be due to active lupus. If a new feature has developed since the last assessment, it should be scored as new (i.e. 4), even if it has subsequently improved or resolved.

GENERAL
Score: 1) Improving
2) Same
3) Worse
4) New
1. Pyrexia (documented) Score: _____
2. Weight loss, unintentional, > 5% in 1 month _____
3. Lymphadenopathy / splenomegaly _____
4. Fatigue / malaise / lethargy _____
5. Anorexia / mausea / vomiting _____

MUCOCUTANEOUS
Score: 1) Improving
2) Same
3) Worse
4) New
6. Maculopapular eruption – severe, active (discoid / bullous) Score: _____
7. Maculopapular eruption – mild _____
8. Active discoid lesions – generalized, extensive _____
9. Active discoid lesions – local, including lupus profundus _____
10. Alopecia – severe, active _____
11. Alopecia – mild _____
12. Panniculitis, severe _____
13. Angio-oedema _____
14. Extensive mucosal ulceration _____
15. Small mucosal ulcers _____
16. Malar erythema _____
17. Subcutaneous nodules _____
18. Perniotic skin lesions _____
19. Peri-ungal erythema _____
20. Swollen fingers Yes ___No ___
21. Sclerodactyly Yes ___No ___
22. Calcinosis Yes ___No ___
23. Telangiectasia Yes ___No ___

NEUROLOGICAL
Score: 1) Improving
2) Same
3) Worse
4) New
24. Impaired level of consciousness Score: _____
25. Psychosis or delirium or confusional state _____
26. Seizures _____
27. Stroke or stroke syndrome _____
28. Aseptic meningitis _____
29. Mononeuritis multiplex _____
30. Ascending or transverse myelitis _____
31. Peripheral or cranial neuropathy _____
32. Disc swelling / cytoid bodies _____
33. Chorea _____
34. Cerebellar ataxia _____
35. Headaches – severe, unremitting _____
36. Organic depressive illness _____
37. Organic brain syndrome including pseudotumor cerebri _____
38. Episodic migranous headaches _____

MUSCULOSKELETAL
Score: 1) Improving
2) Same
3) Worse
4) New
39. Definitive myositis (Bohan and Peter) Score: _____
40. Severe polyarthritis – with loss of function _____
41. Arthritis (definitive synovitis) _____
42. Tendonitis _____
43. Mild chronic myositis _____
44. Arthralgia _____
45. Myalgia _____
46. Tendon contractures and fixed deformity Yes ___No ___
47. Aseptic necrosis Yes ___No ___

CARDIOVASCULAR AND RESPIRATORY
Score: 1) Improving
2) Same
3) Worse
4) New
48. Pleuropericardial pain Score: _____
49. Dyspnea _____
50. Cardiac failure _____
51. Friction rub _____
52. Effusion (pericardial or pleural) _____
53. Mild or intermittent chest pain _____
54. Progressive chest x-ray changes – lung fields _____
55. Progressive chest x-ray changes – heart size _____
56. Electrocardiogram evidence of pericarditis or myocarditis _____
57. Cardiac arrhythmias including tachycardia > 100 bpm in absence of fever _____
58. Pulmonary function fall by > 20% _____
59. Cyto-histological evidence of inflammatory lung disease _____

VASCULITIS
Score: 1) Improving
2) Same
3) Worse
4) New
60. Major cutaneous vasculitis including ulcers Score: _____
61. Major abdominal crisis due to vasculitis _____
62. Recurrent thromboembolism (excluding stroke) _____
63. Raynaud's phenomenon _____
64. Livedo reticularis _____
65. Superficial phlebitis _____
66. Minor cutaneous vasculitis (nailfold, digital, purpura, urticaria) _____
67. Thromboembolism (excluding stroke) – 1st episode Yes ___No ___

RENAL
Answer with number (value) or Yes/No where appropriate
68. Systolic blood pressure (mmHg) Answer:_____
69. Diastolic blood pressure (mmHg) _____
70. Accelerated hypertension Yes ___No ___
71. Urine dipstick (protein 1+ = 1, 2+ = 2, 3+ = 3) _____
72. 24 hour urine protein (grams) _____
73. Newly documented proteinuria of > 1 gram / 24 hours Yes ___No ___
74. Nephrotic syndrome Yes ___No ___
75. Creatinine (plasma/serum) _____
76. Creatinine clearance / glomerular filtration rate _____
77. Active urinary sediment Yes ___No ___
78. Histological evidence of active nephritis (within 3 months) Yes ___No ___

If abnormal value (from above), was this due to lupus ?
68. Yes ___ No ___
69. Yes ___ No ___
71. Yes ___ No ___
72. Yes ___ No ___
75. Yes ___ No ___
76. Yes ___ No ___

HEMATOLOGY
Answer with number (value) or Yes/No where appropriate
79. Hemoglobin (g/dL) _____
80. Total white cell count x 10^9/L _____
81. Neutrophils x 10^9/L _____
82. Lymphocytes x 10^9/L _____
83. Platelets x 10^9/L _____
84. Evidence of active hemolysis Yes ___No ___
85. Coombs test positive Yes ___No ___
86. Evidence of circulating anticoagulant Yes ___No ___

If abnormal value (from above), was this due to lupus?
79. Yes ___ No ___
80. Yes ___ No ___
81. Yes ___ No ___
82. Yes ___ No ___
83. Yes ___ No ___
85. Yes ___ No ___

Adapted from Hay EM, Bacon PA, Gordon C, *et al.* The BILAG index: a reliable and valid instrument for measuring clinical disease activity in SLE. *Q J Med* 1993; 86: 447-58.

Table VI. Systemic Lupus Activity Measure (SLAM) Index.

CONSTITUTIONAL

1. Weight loss Score: _____
   - 0: Absent
   - 1: ≤ 10% body weight
   - 3: > 10% body weight
   - _____ Unknown

2. Fatigue Score:_____
   - 0: Absent
   - 1: Little or no limit on normal activity
   - 2: Limits normal activity
   - _____ Unknown

3. Fever Score:_____
   - 0: Absent
   - 1: 37.5 – 38.5º C or 99.5 – 101.3º F
   - 3: > 38.5º C or > 101.3º F
   - _____ Unknown

INTEGUMENT

4. Oral/nasal ulcers, periungal erythema, malar rash, photosensitive rash, or nailfold infarct Score:_____
   - 0: Absent
   - 1: Present
   - _____ Unknown

5. Alopecia Score:_____
   - 0: Absent
   - 1: Hair loss with trauma
   - 2: Alopecia observed
   - _____ Unknown

6. Erythematous, macular or papular rash, discoid lupus, lupus profundus, or bullous lesions Score: _____
   - 0: Absent
   - 1: < 20% Total Body Surface Area (TBA)
   - 2: 20 – 50% TBA
   - 3: > 50% TBA
   - _____ Unknown

7. Vasculitis (leukocytoclastic vasculitis, urticaria, palpable purpura, livedo reticularis, ulcer or panniculitis) Score:_____
   - 0: Absent
   - 1: < 20% TBA
   - 2: 20 – 50% TBA
   - 3: > 50% TBAor necrosis
   - _____ Unknown

EYE

8. Cytoid bodies Score:_____
   - 0: Absent
   - 1: Present
   - 3: Visual acuity < 20/200
   - _____ Unknown

9. Hemorrhages (retinal or choroidal) or episcleritis Score:_____
   - 0: Absent
   - 1: Present
   - 3: Visual acuity < 20/200
   - _____ Unknown

10. Papillitis or pseudotumor cerebri Score:_____
    - 0: Absent
    - 1: Present
    - 3: Visual acuity < 20/200 or field cut
    - _____ Unknown

RETICULOENDOTHELIAL

11. Lymphadenopathy Score:_____
    - 0: Absent
    - 1: Shotty
    - 2: Diffuse or nodes > 1 cm x 1.5 cm
    - _____ Unknown

12. Hepato- or splenomegaly Score:_____
    - 0: Absent
    - 1: Palpable only with inspiration
    - 2: Palpable without inspiration
    - _____ Unknown

PULMONARY

13. Pleurisy / pleural effusion Score:_____
    - 0: Absent
    - 1: Shortness of breath or pleuritic chest pain
    - 2: Shortness of breath or pleuritic chest pain with exercise
    - 3: Shortness of breath or pleuritic chest pain at rest
    - _____ Unknown

14. Pneumonitis Score:_____
    - 0: Absent
    - 1: X-ray infiltrates only
    - 2: Shortness of breath with exercise
    - 3: Shortness of breath at rest
    - _____ Unknown

CARDIOVASCULAR

15. Raynaud's phenomenon Score:_____
    - 0: Absent
    - 1: Present
    - _____ Unknown

16. Hypertension (diastolic pressure, mmHg) Score:_____
    - 0: < 90
    - 1: 90 – 104
    - 2: 105 – 114
    - 3: > 115
    - _____ Unknown

17. Pericarditis / carditis Score:_____
    - 0: Absent
    - 2: Positional chest pain or arrhythmia
    - 3: Myocarditis with hemodynamic compromise and/or arrhythmia
    - _____ Unknown

GASTROINTESTINAL

18. Abdominal pain (serositis, pancreatitis, or ischemic bowel, etc) Score:_____
    - 0: Absent
    - 1: Complaint
    - 2: Limiting pain
    - 3: Peritoneal signs / ascites
    - _____ Unknown

NEUROMOTOR

19. Stroke syndrome, includes mononeuritis multiplex (MM), reversible neurologic deficit (RND), cerebrovascular accident (CVA), or retinal vascular occlusion (RVO) Score:_____
    - 0: Absent
    - 2: RND, MM, cranial neuropathy or chorea
    - 3: CVA, myelopathy, or RVO
    - _____ Unknown

20. Seizure Score:_____
    - 0: Absent
    - 2: 1 or more per month
    - 3: Status epilepticus
    - _____ Unknown

21. Cortical dysfunction Score:_____
    - 0: Absent
    - 1: Mild depression, personality disorder, or cognitive deficit
    - 2: Change in sensorium, severe depression, or limiting cognitive impairment
    - 3: Psychosis, dementia, or coma
    - _____ Unknown

22. Headache (including migraine equivalents and aseptic meningitis) Score:_____
    - 0: Absent
    - 1: Symptoms only
    - 2: Interferes with normal activities / aseptic meningitis
    - _____ Unknown

23. Myalgia / Myositis Score:_____
    - 0: Absent
    - 1: Symptoms only
    - 2: Limits some activity
    - 3: Incapacitating
    - _____ Unknown

JOINTS

24. Joint pain Score:_____
    - 0: Absent
    - 1: Arthralgia only
    - 2: Objective synovitis
    - 3: Limits function
    - _____ Not recorded

LABORATORY

25. Hematocrit (mg/dL) Score:_____
    - 0: > 35
    - 1: 30 – 35
    - 2: 25 – 29
    - 3: < 25
    - _____ Not recorded

Table VI *(cont.)*. Systemic Lupus Activity Measure (SLAM) Index.

26. White blood cell count (per mm^3) Score:_____
0: > 3500
1: 2000 – 3500
2: 1000 – 1999
3: < 1000
_____ Not recorded

27. Lymphocyte count (per mm^3) Score:_____
0: 1500 – 4000
1: 1000 – 1499
2: 500 – 999
3: < 500
_____ Not recorded

28. Platelet count (x 1000 per mm^3) Score:_____
0: > 150
1: 100 – 149
2: 50 – 99
3: < 50
_____ Not recorded

29. Westergren ESR (mm/hr) Score:_____
0: < 25
1: 25 – 50
2: 51 – 75
3: > 75
_____ Not recorded

30 Serum creatinine (mg/dL) or creatinine clearance (% normal) Score:_____
0: 0.5 – 1.3 or 80 – 100%
1: 1.4 – 2.0 or 60 – 79%
2: 2.1 – 4.0 or 30 – 59%
3: > 4.0 or < 30%
_____ Not recorded

31. Urine sediment (per high power field) Score:_____
0: Normal
1: 6 – 10 RBC or 6 – 10 WBC; OR 0-3 granular or 0-3 non RBC casts; OR trace – 1+ protein (<500 mg/L24 hr urine protein)
2: 11 – 25 RBC or 11 – 25 WBC; OR >3 granular or >3 non RBC casts; OR 2 – 3+ protein (>500 mg – 3.5 g/L24 hr urine protein)
3: > 25 RBC or > 25 WBC; OR any RBC casts; OR 4+ protein > 3.5 g/L24 hr urine protein)

Adapted from Liang HL, Socher SA, Larson MA, and Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1989; 32: 1107-18.

are often not associated with any serologic marker. The ANAis not useful for assessing disease activity, and therefore should be obtained only once, unless a laboratory error is suspected. It is for classification purposes only.

Standardized measures of disease activity

Because no single measure can describe status in all SLE patients, standardized indices for assessing SLE disease activity have been created. In addition to the Physicians'Global Assessment (an estimate of activity rated on a 0 to 3 visual analog scale), the most common measures used include the SLE Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG), the Systemic Lupus Activity Measure (SLAM), the Lupus Activity Index (LAI) (40, 41), and the European Consensus Lupus Activity Measurement (ECLAM). All of these indices are valid, reliable, and comparable. Some of them are easy to incorporate into routine clinical care, giving a quick snapshot of a patient's status (41).

The SLEDAI is perhaps the easiest assessment tool to use (Table IV) (42). Twenty-four features that are attributed to lupus are listed, with a weighted score given to any one that is present. The more serious manifestations (such as renal, neurologic, and vasculitis) are weighted more than others (such as cutaneous manifestations). The maximum possible score is 105. Recent revisions have been proposed that emphasize ongoing disease, not just new or recurrent activity (SELENA-SLEDAI and SLEDAI 2001) (40).

The BILAG index (Table V) is more comprehensive than the SLEDAI, recording clinical disease activity in 8 different organ systems for a total of 86 items (43). Each item is measured qualitatively by clinical observation (yes/no, improving/same/worse/new) or quantitatively by measuring hematologic and renal lab values. Based on these items, each of the 8 organ systems is allocated an alphabetical score of A (most active), B (moderate activity), C (minor activity), D (stable), or E (never present). Normally, a total score is not calculated. However, it can be converted into a disease activity scale by assigning points to the alphabetical score: A = 9, B = 3, C = 1, D = 0, E = 0, with a maximum potential score of 72 (44). While it is the most comprehensive index, software is recommended for calculating scores, making it cumbersome to use in a clinical setting. Hence, it is more apt for clinical trials and clinical research. In addition, it misses ophthalmologic and gastrointestinal features that are covered in some of the other indices. It also does not monitor immunologic serologies.

The SLAM (Table VI) and its modification, SLAM-R, record 10 aspects of SLE disease, totaling 31 features (45). Each is assigned a numerical weight assessed by degrees of severity, with the total sum indicative of overall disease activity (the higher the number, the more active the disease). Like the BILAG, it includes subjective features reported by the patients and excludes immunologic serologies.

The Lupus Activity Index is a concise measure comprised of a 0-3 visual analog scale for 4 symptoms (fatigue, rash, joint involvement, serositis) and 4 signs (neurologic, renal, pulmonary, and hematologic involvement) (41). While its list of SLE features is not comprehensive and its measure of disease activity is not weighted, it provides a simple, broad, and accurate assessment of activity in much the same fashion as the Physicians'Global Assessment.

The European Consensus Lupus Activity Measurement (ECLAM) (Table VII) was developed in 1992 by analyzing the symptoms and laboratory parameters presented by a European cohort of 704 SLE patients. The index contains 15 selected variables weighted according to their respective regression coefficients in a multivariate model. This index differs from other widely used indices because it was directly derived

Table VII. European Consensus Lupus Activity Measurement (ECLAM).

1. Generalised manifestations	Any of the following:	0.5
Fever	Documented basal morning temperature of 37.5°C not due to an infective process.	
Fatigue	Asubjective feeling of extraordinary tiredness.	
2. Articular manifestations	Any of the following:	1
Arthritis	Non-erosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints).	
Evolving arthralgia	New onset or worsening of specific localised pain without objective symptoms in at least two peripheral joints.	
3a. Active muco-cutaneous manifestations	Any of the following:	0.5
Malar rash	Fixed erythema, flat or raised over the malar eminences, and tending to spare the naso-labial folds.	
Generalised rash	Amaculo-papular rash not induced by drugs, that may be located anywhere on the body, and that is not strictly dependent on sun exposure.	
Discoid rash	Erythematosus, raised patches with adherent keratotic scaling and follicular plugging.	
Skin vasculitis	Including digital ulcers, purpura, urticaria, bullous lesions.	
Oral ulcers	Oral or naso-pharyngeal ulcers, usually painless, observed by a physician.	
3b. Evolving mucocutaneous manifestations	If any of the above mucocutaneous manifestations are new or have worsened since the last observation, add 1 point.	1
4. Myositis*	Confirmed by raised muscle enymes and/or EMG examination and/or histology.	2
5. Pericarditis	Documented by ECC or rub or evidence of pericardial effusion on ultrasound	1
6. Intestinal manifestations	Any of the following:	2
Intestinal vasculitis	Evidence of acute intestinal vasculitis.	
Sterile peritonitis	Evidence of abdominal effusion in the absence of infective processes.	
7. Pulmonary manifestations	Any of the following:	1
Pleurisy	Clinical or radiological evidence of pleural effusion in the absence of infective processes.	
Pneumonitis	Single or multiple lung opacities on chest X-ray thought to reflect active disease not due to and infective process.	
Ingravescent dyspnoea	Due to an evolving interstitial involvement.	
8. Evolving neuropsychiatric manifest.*	New appearance or worsening of any of the following:	2
Headache/migraine	Recently developed, persistent or recurrent. Poorly responsive to the most commonly used drugs, but partially or totally responsive to corticosteroids.	
Seizures	Grand mal or petit mal seizures, Jacksonian fits, temporal lobe seizures, or choreic syndrome, in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis or electrolyte inbalance).	
Stroke	Cerebral infarction or haemorrhage, instrumentally confirmed	
Organic brain disease	Impairment of memory, orientation, perceprion, and ability to calculate.	
Psychosis	Dissociative features in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance.	
9a. Renal manifestations*+	Any of the following:	0.5
Proteinuria	At least 500 mg/day.	
Urinary casts	Red cells, haemoglobin, granular, tubular or mixed casts.	
Haematuria	Microscopic or macroscopic.	
Raised serum creatinine or reduced creatinine clearance		
9b. Evolving renal manifestations	If any of the above renal manifestations are new or have worsened since the last two observations, add 2 points.	
10. Haematologic features	Any of the following:	1
Non-haemolytic anaemia	ACoombs-negative normocytic hypochromic or normochromic anaemia without reticulocytosis.	
Haemolytic anaemia*	ACoombs-positive haemolytic anaemia, with reticulocytosis and elevated LDH, in the absence of offending drugs.	
Leukopenia (or lymphopenia)	Less than 3,500/mm^3 WBC (or 1,500/mm^3 lymphocytes) in the absence of offending drugs.	
Thrombocytopenia	Less than 100,000/mm^3 in the absence of offending drugs.	
11. Erythrocyte sedimentation rate		1
Raised ESR	> 25 mm/h by Westergren or comparable methods, not due to other concomitant pathological process	
12a. Hypocomplementaemia	Reduced plasma level of any of the following:	1
C3	By radial immunodiffusion or laser nephelometer.	
CH50	By standardised haemolytic methods.	
12b. Evolving hypocomplementaemia	Significantly reduced level of any of the items mentioned above (plus C4) with respect to the last observation.	1
FINALSCORE #		

* If this system (or manifestation) is the only involvement present from among items 1 - 10, add 2 more points. + Excluding patients with end-stage chronic renal disease. # If the final total score is not an integer number, round off to the lower integer for values < 6 and to the higher integer for values > 6. If the final total score is > 10, round off to 10. Adapted from reference 46.

from the study of a large number of actual patients. The definition of disease activity obtained can be considered as the average definition of this entity in Europe (46).

The validity, reliability and sensitivity to change of the ECLAM have been confirmed by different authors (47). In a recent study Liang *et al*. have showed that the ECLAM index as well as the other measures studied (namely the BILAG, ECLAM, SLAM-R, SLEDAI, SELENA-SLEDAI, RIFLE) demonstrated discriminatory properties more than sufficient for use in clinical trials (48). Furthermore the index has shown a high construct validity and sensitivity to change in the assessment of childhood SLE (49). A modified version for use in pregnancy is also available.

Finally, in 2000 the ECLAM index was validated for the retrospective calculation of disease activity from the data provided in patients' clinical charts (50).

A computerized programme is now available to collect clinical and laboratory data on SLE patients and automatically calculate the following activity indices: BILAG, ECLAM, SLAM, SLEDAI SIS.

In the Hopkins Lupus Cohort, a prospective cohort study of predictors of disease activity, damage, and health status in SLE with over 1000 patients currently enrolled into the database, three measures are used for each patient at each quarterly visit: the Physicians' Global Assessment, the Lupus Activity Index, and the SLEDAI (51).

Assessing chronic damage of SLE

With improved understanding of the pathophysiology of SLE and with improved therapies, survival has increased over time. However, a substantial amount of organ damage may accumulate throughout a patient's life, and management of later complications of disease is required.

In 1996, a damage index for SLE was developed by the Systemic Lupus International Collaborating Clinics (SLICC) and endorsed by the ACR; hence, it has become known as the SLICC/ACR Damage Index (Table VIII) (52). There is international consensus that it is the best instrument to measure organ

Table VIII. Systemic Lupus International Collaborating Clincs/American College of Rheumatology (SLICC/ACR) Damage Index.

Score	Item
	Ocular (either eye, by clinical assessment)
0,1	Any cataract ever
0,1	Retinal change or optic atrophy
	Neuropsychiatric
0,1	Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis
0,1	Seizures requiring therapy for 6 months
0,1,2	Cerebrovascular accident ever (score 2 if >1)
0,1	Cranial or peripheral neuropathy (excluding optic)
0,1	Transverse myelitis
	Renal
0,1	Estimated or measured glomerular filtration rate < 50%
0,1	Proteinuria > 3.5g/24h
or 3	OR End-stage renal disease (regardless of dialysis or transplantation)
	Pulmonary
0,1	Pulmonary hypertension (right ventricular prominence, or loud P2)
0,1	Pulmonary fibrosis (physical and radiograph)
0,1	Shrinking lung (radiograph)
0,1	Pleural fibrosis (radiograph)
0,1	Pulmonary infarction (radiograph)
	Cardiovascular
0,1	Angina OR coronary artery bypass
0,1,2	Myocardial infarction ever (score 2 if > 1)
0,1	Cardiomyopathy (ventricular dysfunction)
0,1	Valvular disease (diastolic murmur or systolic murmur > 3/6)
0,1	Pericarditis for 6 months, OR pericardectomy
	Peripheral vascular
0,1	Claudication for 6 months
0,1	Minor tissue loss (pulp space)
0,1,2	Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site)
0,1	Venous thrombosis with swelling, ulceration, OR venous stasis
	Gastrointestinal
0,1,2	Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if > 1 site)
0,1	Mesenteric insufficiency
0,1	Chronic peritonitis
0,1	Stricture OR upper gastrointestinal tract surgery ever
0,1	Chronic pancreatitis
	Musculoskeletal
0,1	Muscle atrophy or weakness
0,1	Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)
0,1	Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)
0,1,2	Avascular necrosis (score 2 if > 1)
0,1	Osteomyelitis
0,1	Tendon rupture
	Skin
0,1	Scarring chronic alopecia
0,1	Extensive scarring of panniculum other than scalp and pulp space
0,1	Skin ulceration (excluding thrombosis for > 6 months)
0,1	**Premature gonadal failure**
0,1	**Diabetes** (regardless of treatment)
0,1,2	**Malignancy** (exclude dysplasia) (score 2 if >1 site)

Adapted from Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39:363-9.

damage after the diagnosis of lupus. In it, 12 systems are assessed by 41 items for damage, which is defined as non-reversible change that is not related to active inflammation and that has occurred since the onset of lupus, ascertained by clinical assessment and present for at least 6 months. If evidence of damage is noted for a particular item, it is given a score of 1. Some items may score 2 points if they occur more than once, so that the maximum possible score is 47. Scores can only increase with time, but scores rarely reach over 12.

The SLICC/ACR Damage Index has been validated and proven to be reliable (**53**). Higher damage index scores early in disease have been associated with a poor prognosis and with increased mortality (40). Thus, the SLICC/ACR Damage Index complements other measures of disease activity described above, and it is an important outcome measure. It is usually completed (or updated) yearly.

Assessing the health status of SLE patients

The diagnosis, assessment of disease activity, and assessment of chronic damage of SLE are primarily performed by the physician. However, an equally important component is the patient's own perception of his or her health and quality of life. Assessing this is often complex, time-consuming, and requires data manipulation before impacting clinical decisions. To date, no measures have been created specifically for SLE.

The Short-Form-36 (SF-36) is currently the most widely used and comprehensive index for this purpose in SLE. It was originally constructed in 1992 to survey health status in the Medical Outcomes Study (54). Since then, its design has been applicable to clinical practice, research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions.

In SLE, more detailed and supplemental questionnaires have been used to further characterize symptoms such as fatigue, stress, depression, psychological distress, physical disability, and quality of life (55). Interestingly, health status correlated most strongly with psychosocial factors and less with disease activity and damage (56). The most important determinant of overall health status in SLE may be fibromyalgia (57). This would suggest that addressing coping strategies and providing social support systems may prove as powerful as pharmacologic management in treating SLE patients.

Conclusion

The assessment of SLE is marked by four components: accurate diagnosis, monitoring of disease activity, recording of accumulated damage, and integration of these with the patient's own perceptions of health status and quality of life. Multiple standardized measures have been developed for each component, many of which are effective in routine clinical practice. A detailed history, thorough physical examination, and appropriate use of laboratory and radiographic studies are required at each clinic visit to fully assess SLE. Quarterly follow-up is recommended even for the stable SLE patient. With the complex phenotype and variable disease course of SLE, all four components are equally important and essential in improving the morbidity, mortality, and quality of life in SLE.

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