ARTHRITIS & RHEUMATISM
Vol. 42, No. 9, September 1999, pp 1785–1796

Arthritis & Rheumatism

Official Journal of the American College of Rheumatology

SPECIAL ARTICLE

GUIDELINES FOR REFERRAL AND MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS IN ADULTS

AMERICAN COLLEGE OF RHEUMATOLOGY AD HOC COMMITTEE ON SYSTEMIC LUPUS ERYTHEMATOSUS GUIDELINES

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown etiology, with protean manifestations and a variable course and prognosis. SLE is a complex disorder that affects primarily women in their childbearing years. It is characterized by periods of relative quiescence and periods of exacerbations, which may involve any organ or system in various combinations (1–10) (Tables 1 and 2). Patients with SLE develop distinct immunologic abnormalities, in particular, antinuclear, anticytoplasmic, and antiphospholipid antibodies. Genetic, immunologic, hormonal, and environmental factors are involved in its pathogenesis (1–10). The prevalence of SLE is 1:1,000; thus, most primary care physicians and general internists will not have sufficient experience in the management of moderate or severe life-threatening disease.

Members of the Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines are as follows. Dafna D. Gladman, MD (chair), Murray B. Urowitz, MD: The Toronto Hospital and University of Toronto, Toronto, Ontario, Canada; John M. Esdaile, MD, MPH: Mary Pack Arthritis Centre and Vancouver Hospital, Vancouver, British Columbia, Canada; Bevra H. Hahn, MD: University of California, Los Angeles; John Klippel, MD: National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland; Robert Lahita, MD, PhD: Saint Vincent's Medical Center, New York, New York; Matthew H. Liang, MD, MPH, Peter Schur, MD: Brigham and Women's Hospital, Boston, Massachusetts; Michelle Petri, MD, MPH: Johns Hopkins Hospital, Baltimore, Maryland; Daniel Wallace, MD: Cedars–Sinai Medical Center/University of California, Los Angeles, School of Medicine.

Address reprint requests to American College of Rheumatology, 1800 Century Place, Suite 250, Atlanta, GA 30345.

Submitted for publication January 29, 1999; accepted in revised form May 18, 1999.

In addition to the persistent risk of disease flares, more than one-half of SLE patients develop permanent organ system damage (11). This damage progresses over time and is usually more severe in African American patients than in white patients (12). Although the prognosis of SLE has improved dramatically in the last 4 decades, mortality remains a major concern. The mortality rate among patients with SLE is at least 3 times that of the general population (13). Survival rates are ~80% at 10 years after diagnosis and ~65% at 20 years (1–8,13–16). Deaths early in the course of SLE are usually attributed to active disease and infections, but deaths that occur later in the disease course are often due to atherosclerotic vascular disease (14). Therapy, especially long-term high-dose glucocorticoid treatment, can contribute to myopathy, osteoporosis, hypertension, diabetes, atherosclerotic vascular disease, infections, and death. Timely and aggressive therapy, however, can delay or prevent morbidity and organ failure and is cost effective (17).

SLE is a systemic illness with multiple end-organ involvement. As such, it challenges both the patients and their families. Patients with newly diagnosed SLE often have anxieties about a possibly fatal chronic illness with unpredictable flares and potential disability; these anxieties should be addressed. Patients must learn how to cope with and monitor their own disease and to assist the physician in distinguishing coincident unrelated symptoms from signs and symptoms of a flare. Psychological support by either the physician and/or an appropriate health professional is essential. SLE patients may need the expertise of professionals in the fields of social work, vocational counseling, psychology, physical and occupational therapy, ophthalmology, dermatology, nephrol-

Table 1. Clinical features of systemic lupus erythematosus

System	Features
Constitutional	Fatigue Fever (in the absence of infection) Weight loss
Musculoskeletal	Arthritis, arthralgia Myositis
Skin	Butterfly rash Photosensitivity Mucous membrane lesion Alopecia Raynaud's phenomenon Purpura Urticaria Vasculitis
Renal	Hematuria Proteinuria Casts Nephrotic syndrome
Gastrointestinal	Nausea, vomiting Abdominal pain
Pulmonary	Pleurisy Pulmonary parenchyma Pulmonary hypertension
Cardiac	Pericarditis Endocarditis Myocarditis
Reticuloendothelial	Lymphadenopathy Splenomegaly Hepatomegaly
Hematologic	Anemia Thrombocytopenia Leukopenia
Neuropsychiatric	Psychosis Seizures Organic brain syndrome Transverse myelitis Cranial neuropathies Peripheral neuropathies

ogy, cardiology, orthopedic surgery, and other disciplines. Not all of these are needed at any one time, and their coordination is best done by a specialist, usually a rheumatologist, who has experience in following up patients with SLE and knows what value is added from these consultants.

These guidelines for the management of SLE were prepared to improve the quality of care for SLE patients by primary care physicians. They are based on available evidence-based information for the diagnosis and management of the disease. Where such evidence is unavailable, the guidelines are based on the recommendations of SLE specialists. While the members of the American College of Rheumatology Ad Hoc Committee

Table 2. Frequency of serologic abnormalities in systemic lupus erythematosus*

Abnormality	At onset, %	At any time, %
Antinuclear antibodies	76	94
Antibodies to		
Double-stranded DNA	34	71
Sm	31	49
RNP	21	35
Ro/SSA	33	67
La/SSB	27	49
Low complement	44	77

* From ref. 5.

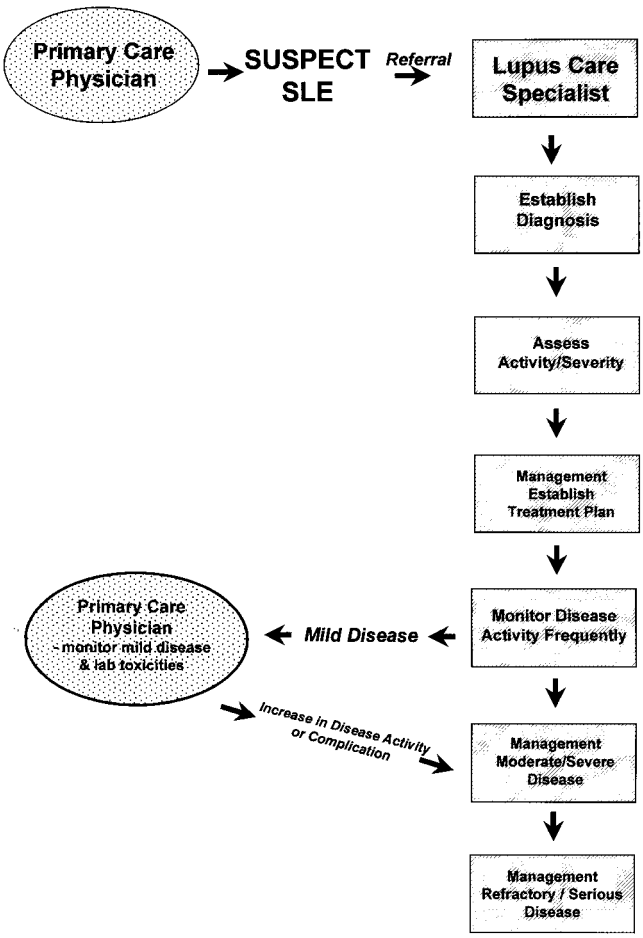

Figure 1. Tasks of the primary care physician in the diagnosis and management of systemic lupus erythematosus (SLE).

Table 3. 1997 update of the 1982 American College of Rheumatology classification criteria for systemic lupus erythematosus*

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	a. Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria >0.5 gm per day or >3+ if quantitation not performed *OR* b. Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	a. Seizures—in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b. Psychosis—in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	a. Hemolytic anemia with reticulocytosis *OR* b. Leukopenia—<4,000/mm^3 on ≥2 occasions *OR* c. Lymphopenia—<1,500/mm^3 on ≥2 occasions *OR* d. Thrombocytopenia—<100,000/mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer *OR* b. Anti-Sm: presence of antibody to Sm nuclear antigen *OR* c. Positive finding of antiphospholipid antibodies based on: 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive test result for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug

* From ref. 10.

on SLE Guidelines were rheumatologists who are experts in the care of patients with SLE, the guidelines were reviewed by primary care physicians who concurred with their content.

The 4 major tasks of the primary care physician in the diagnosis and management of SLE (Figure 1) are 1) to be alert to the possibility of SLE in their patients, and to make a diagnosis as early as possible; 2) to manage and monitor patients with SLE who have mild and stable disease (i.e., those without major organ involvement and/or comorbidity); 3) to recognize when referral to a rheumatologist is indicated; and 4) to collaborate with the specialist in monitoring disease activity and therapy in patients with moderate to severe SLE.

Initial evaluation: making the diagnosis

Because of its multisystem involvement and its protean manifestations, the diagnosis of SLE may be difficult. SLE should be suspected in any patient who has features affecting 2 or more organ systems as listed in Table 1. The American College of Rheumatology has

Table 4. Conditions that may be confused with systemic lupus erythematosus

Undifferentiated connective tissue disease
Sjögren's syndrome
Antiphospholipid antibody syndrome
Fibromyalgia with positive antinuclear antibody
Idiopathic thrombocytopenia purpura
Drug-induced lupus
Early rheumatoid arthritis
Vasculitis

published criteria for the classification of patients as having SLE (9,10), shown in Table 3. Although the criteria were designed to ensure that SLE patients reported in the literature do in fact have the disease, they are also useful in evaluating individual patients. If a patient has, at any time in his or her medical history, 4 of the 11 criteria documented, the diagnosis of SLE can be made with ~95% specificity and 85% sensitivity (18,19). If the patient meets fewer than 4 criteria, the diagnosis of SLE is possible (for example, a young woman with nephritis, antinuclear antibodies [ANA], and anti-DNA meets only 3 criteria but almost surely has SLE), and the diagnosis depends upon clinical judgment. If ANA are negative, the patient has a very low probability of having SLE. Patients with positive ANA alone, without organ system involvement or typical laboratory findings, are unlikely to have SLE (20).

Other serologic tests may have a higher predictive value than ANA, and thus may aid in the diagnosis of SLE or related connective tissue disease. High-titer IgG antibodies to double-stranded DNA (dsDNA) and antibodies to the Smith antigen (anti-Sm) are usually specific for SLE. Antibodies to RNA proteins (anti-RNP, anti-Ro, anti-La) and to phospholipids (anticardiolipin) occur in SLE and other connective tissue diseases, as does hypocomplementemia (18,21). The frequencies at which these serologic abnormalities occur in SLE are listed in Table 2.

A number of other diseases may be confused with early SLE because they present with either clinical or laboratory features that may be similar to those seen in SLE. These include undifferentiated connective tissue disease, primary Sjögren's syndrome, primary antiphospholipid syndrome, fibromyalgia with positive ANA, idiopathic thrombocytopenic purpura, drug-induced lupus, and early rheumatoid arthritis (22) (Table 4). SLE can be mild, moderate, or severe. Almost all patients with anything more than stable mild symptoms should be cared for by an experienced physician, who, in most cases, will be a rheumatologist. Many SLE patients may also prefer to have their specialist act as principal care provider to manage and coordinate their general health care. At any one time, one or more organ systems may be affected by SLE. Patients with mild SLE are those who 1) clearly have the diagnosis, 2) are clinically stable, 3) do not have life-threatening disease, and 4) have stable normal function of body systems that can be damaged by SLE, such as kidneys, skin, joints, hematologic system, lung, heart, gastrointestinal (GI) tract, and central nervous system (CNS). In addition, the patient should have no significant toxicities from therapies for SLE. This definition of mild SLE is reviewed in Table 5.

Table 5. Characteristics of patients with mild systemic lupus erythematosus (SLE)

1. Diagnosis of SLE is confirmed or highly suspected.
2. Disease is clinically stable.
3. Disease is not life-threatening.
4. Body systems that can be a target of SLE have normal and stable function, including
a. Kidneys
b. Skin
c. Joints
d. Hematologic system
e. Lungs
f. Heart
g. Gastrointestinal system
h. Central nervous system
5. There are not significant toxicities of the therapies for SLE.

Referral

We recommend referral to a rheumatologist and/or other appropriate specialist for the following purposes (Figure 1 and Table 6).

Establishment of the diagnosis. Patients in whom SLE is suspected based on history, physical examination results, or laboratory data should be referred to a rheumatologist to establish or confirm the diagnosis, particularly if there are symptoms, signs, or laboratory evidence of disease that suggest more than mild SLE (Table 5). As noted above, diagnosis can be difficult because of multisystem involvement and variability of

Table 6. Reasons for referral to a rheumatologist

1. To confirm a diagnosis
2. To assess disease activity and severity
3. To provide general disease management
4. To manage uncontrolled disease
5. To manage organ involvement or life-threatening disease
6. To manage/prevent treatment toxicities
7. In other specific circumstances, including antiphospholipid syndrome, pregnancy, surgery

presentation of the disease. Thus, in most cases, a rheumatologist may be needed to interpret laboratory findings and confirm the diagnosis.

Assessment of disease activity and severity. Assessment of disease activity and severity is important for the establishment of an appropriate treatment program for an individual patient. Since patients with very active and severe disease are likely to require ongoing care by a rheumatologist, it is necessary to assess both the activity and the severity of the disease early on. Validated indices have been developed for the assessment of both disease activity and disease severity (15,23).

Establishment of a plan for disease management. A patient with established SLE may be referred to an appropriate specialist to establish a treatment plan that may then be followed by the primary care physician if the disease remains stable and mild. SLE patients may be referred to a rheumatologist to monitor efficacy and toxicity of treatment (e.g., antimalarial drugs, glucocorticoids, and immunosuppressive/cytotoxic drugs) or to provide patient education. In addition, the rheumatologist may be asked to coordinate care with allied health professionals and other medical specialists. Patients for whom complicated management decisions are necessary should be referred to a rheumatologist or other appropriate specialist depending on the major organ system involved. Examples of such complicated management decisions are the requirement for long-term glucocorticoid therapy to control the disease; prevention of the development of complications from glucocorticoid therapy or planning treatment of those complications; the need to consider therapy with sex hormones, antimalarial agents, or immunosuppressive/cytotoxic drugs; and consideration of investigational treatment modalities such as apheresis, intravenous gamma globulin, dapsone, dehydroepiandrosterone (DHEA), and new experimental therapies.

Management of uncontrolled disease. In patients whose SLE manifestations persist despite therapy, consultation with a rheumatologist or other appropriate specialist, depending on the organs involved, is required. Examples of uncontrolled disease include pleurisy, pericarditis, and/or arthritis not controlled by nonsteroidal antiinflammatory drugs (NSAIDs); rash not controlled by topical therapy; active vasculitis; digital ulcers; muscle weakness and/or elevated creatine phosphokinase (CPK) despite steroid therapy; any CNS manifestation; and continuing evidence of active renal disease, cardiopulmonary disease, or hematologic manifestations despite therapy. The specific management for such patients is best provided by specialists, and is reviewed briefly below in the section on the treatment of severe SLE. Persistent laboratory abnormalities such as hypocomplementemia or high-titer anti-DNA may also suggest underlying uncontrolled disease and constitute a reason for referral. When patients demonstrate a persistent need for dosages of medication so high that side effects are likely to occur, they should be referred to an experienced consultant.

Management of disease with major organ damage. Patients demonstrating end-organ compromise should be referred to a rheumatologist or other appropriate specialist depending on the organ(s) involved. Examples include GI involvement with motility disorders or ischemia, lung involvement causing shortness of breath, pulmonary hypertension, malignant hypertension, renal insufficiency, nephrotic syndrome, severe peripheral or CNS disease (e.g., psychosis, confusion, disorientation, paresthesias, seizure, cognitive dysfunction, severe unremitting headache, cerebrovascular accident, transient ischemic attack, retinal vasculitis), muscle atrophy or weakness, deforming arthritis, osteoporosis (with fracture), avascular necrosis of bone, and severe skin involvement (scarring, alopecia, ulcers) (11).

Management/prevention of complications of therapies. In some patients, the treatment is effective but drug toxicity or intolerance occurs. These patients may present with serious infections, steroid myopathy, avascular necrosis of bone, hypertension, osteoporosis, diabetes, cushingoid appearance, GI intolerance, and persistent cytopenias (see Table 7).

Management of special clinical situations. There are special conditions that pose additional problems for the SLE patient and necessitate close observation and frequent alteration of drug regimens. Appropriate consultation is recommended. Some of these conditions, and reasons for close observation and consultation, are as follows: a*ntiphospholipid antibody syndrome (*management of recurrent fetal loss; venous and/or arterial thrombosis); *pregnancy* (assessment of disease activity, which may be confounded by the normal physiologic and immunologic effects of the pregnancy; management of the gestational and postpartum treatment regimen; risk of neonatal SLE in infants of mothers with antibodies to Ro/SSA and La/SSB); *surgery* (preoperative disease assessment and clearance for surgery; management of the intra- and postoperative treatment regimen [e.g., glucocorticoids, anticoagulants, immunosuppressive/cytotoxic agents]).

Monitoring SLE

Once a diagnosis is established and referral made for any of the above reasons, the following guidelines should be followed by the managing physician(s).

Table 7. Recommended monitoring strategy for drugs commonly used in systemic lupus erythematosus*

Drug	Toxicities requiring monitoring	Baseline evaluation	Monitoring	
			System review	Laboratory
Salicylates, nonsteroidal antiinflammatory drugs	Gastrointestinal bleeding, hepatic toxicity, renal toxicity, hypertension	CBC, creatinine, urinalysis, AST, ALT	Dark/black stool, dyspepsia, nausea/vomiting, abdominal pain, shortness of breath, edema	CBC yearly, creatinine yearly
Glucocorticoids	Hypertension, hyperglycemia, hyperlipidemia, hypokalemia, osteoporosis, avascular necrosis, cataract, weight gain, infections, fluid retention	BP, bone densitometry, glucose, potassium, cholesterol, triglycerides (HDL, LDL)	Polyuria, polydipsia, edema, shortness of breath, BP at each visit, visual changes, bone pain	Urinary dipstick for glucose every 3–6 months, total cholesterol yearly, bone densitometry yearly to assess osteoporosis
Hydroxychloroquine	Macular damage	None unless patient is over 40 years of age or has previous eye disease	Visual changes	Funduscopic and visual fields every 6–12 months
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	CBC, platelet count, creatinine, AST or ALT	Symptoms of myelosuppression	CBC and platelet count every 1–2 weeks with changes in dose (every 1–3 months thereafter), AST yearly, Pap test at regular intervals
Cyclophosphamide	Myelosuppression, myeloproliferative disorders, malignancy, immunosuppression, hemorrhagic cystitis, secondary infertility	CBC and differential and platelet count, urinalysis	Symptoms of myelosuppression, hematuria, infertility	CBC and urinalysis monthly, urine cytology and Pap test yearly for life
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates, fibrosis	CBC, chest radiograph within past year, hepatitis B, C serology in high-risk patients, AST, albumin, bilirubin, creatinine	Symptoms of myelosuppression, shortness of breath, nausea/vomiting, oral ulcer	CBC and platelet count every 4–8 weeks, AST or ALT every 4–8 weeks, albumin every 4–8 weeks, serum creatinine, urinalysis

* CBC = complete blood cell count; AST = aspartate transaminase; ALT = alanine transaminase; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Lifelong monitoring is required for most patients. The cornerstone of managing SLE is lifelong patient monitoring to detect flares of disease early and to institute prompt, appropriate therapy. In patients who have moderate to severe disease at any time, this lifelong monitoring may best be supervised by a physician with experience in treatment of SLE. This is accomplished by seeing patients on a regular basis. A history-taking that emphasizes features of SLE, appropriate physical examination, and laboratory tests are required (for review, see refs. 1–8, 23, and 24) (Table 8). The frequency of these evaluations will depend on the activity, severity, and extent of the SLE, the response to treatment, and the type of treatment, including the need for toxicity monitoring. SLE disease activity can be diagnosed by specific clinical features (e.g., arthritis, serositis, etc.) or laboratory features (e.g., anti-dsDNA antibodies or complement levels), or by using a global activity index.

At routine followup visits, the following should be obtained: complete blood cell count, platelet count, creatinine measurement, and urinalysis, even if the patient has had normal values in the past. Patients with known renal disease should have a urinalysis, 24-hour urine collection for protein, creatinine measurement, complete blood cell count, and determination of cholesterol, calcium, phosphorus, alkaline phosphatase, sodium, and potassium levels approximately once a month at the onset of nephritis and more often if the condition is unstable. Measurement of 24-hour urine protein, creatinine clearance rate, or the more accurate measurement of glomerular filtration rate is useful to indicate response to therapy. In many patients, particularly those

Table 8. Monitoring of patients with systemic lupus erythematosus

History
Fever
Weight change
Fatigue
New rash
Increased hair loss
Pleuritic chest pain
Joint pain and swelling
Physical examination
Joint swelling
Rash, discoid lesions
Alopecia
Mucous membrane ulcers
Vasculitic lesions
Funduscopic examination
Edema
Other features*
Investigations
Hematology
Chemistry
Urinalysis
Serology
Radiology

* As suggested by the history.

with nephritis, it is also useful to monitor serum levels of complement component C3 and anti-dsDNA antibodies at regular intervals (20,21,25–27).

Patients with longstanding SLE can develop new organ system involvement over time (15). This is especially true for renal disease in African Americans. Patients with severe hemolytic anemia require a hematocrit measurement and a reticulocyte count initially weekly. Patients with severe thrombocytopenia ($<50{,}000/mm^3$) require platelet count monitoring initially weekly. The frequency of subsequent laboratory tests in such patients will depend on the response to therapy.

In many SLE patients, changes in the results of certain laboratory tests, such as a decrease in serum complement levels, an increase in anti-dsDNA level, a rise in erythrocyte sedimentation rate, a decrease in hemoglobin level or leukocyte or platelet counts, a rise in CPK level, or the appearance of microscopic hematuria or proteinuria, may precede a clinical disease flare. Modification of treatment at the time a change in laboratory results is noted can significantly reduce the chance of flare (27). The clinician should establish the utility of various tests in an individual patient, then perform those selected tests regularly to detect early flare. In some SLE patients, abnormalities in the results of such tests (particularly antibodies to dsDNA and serum complement levels) do not predict disease activation (28). Monitoring of laboratory findings in patients with SLE may be facilitated by the use of flow charts, particularly for tracking serologic abnormalities. In addition, global activity indices are useful for the assessment of SLE disease activity in the office/clinic setting (15,23).

Finally, it is important to establish a team relationship among all of the health care providers, including primary care physician, specialists, nurses, hospital staff, pharmacists, and the patient and family. This team approach will allow manifestations of disease flares or medication toxicity to be detected at an early stage. The team approach would also facilitate the identification of additional features of the disease such as fibromyalgia (5), which may be confused with disease manifestations but require a different management approach than the treatment of active disease or complications of therapy.

When should a kidney biopsy be performed? Kidney biopsy is indicated for diagnostic purposes in SLE patients in whom nephritis is suspected. Thus, patients with persistent urinary sediment abnormalities such as hematuria and pyuria without adequate explanation (infection, menstrual period, stone), patients who have urinary casts, or patients who have increased serum creatinine levels should have a renal biopsy. The prognostic value of kidney biopsy, although controversial, has been demonstrated, particularly for patients with normal serum creatinine levels (15,24,29). Patients with proliferative glomerular lesions and chronic changes found on kidney biopsy are at a higher risk for end-stage renal disease and death than patients who do not demonstrate these changes. Patients with deteriorating renal function, or patients not responding to conventional therapy, may need a kidney biopsy to outline a course of treatment (29).

Frequency of followup visits. The frequency of followup visits is determined by the activity and severity of the disease and its complications. Patients with very mild stable disease may require followup visits at 3–6-month intervals by a primary care physician, internist, pediatrician, or rheumatologist. Patients with more severe disease or with complications of therapy, as well as patients with active disease, will need more frequent followup, as will patients during pregnancy and postpartum periods. Patients beginning immunosuppressive medication will also require more frequent followup.

Monitoring for treatment toxicity (Tables 7 and 8). All of the medications used in SLE require vigilance to assure their safe use.

Patients taking NSAIDs should be observed for the possibility of GI, liver, and renal toxicity. In addition, several of the NSAIDs infrequently cause aseptic meningitis in patients with SLE (30). Their most serious side

effects are gastritis, gastric ulceration, and GI bleeding. Patients at high risk for these complications should be treated with gastroprotective agents, of which the most effective may be proton pump inhibitors; H_2 blockers and prostaglandin analogs are also acceptable (31).

The role of the newer cyclooxygenase 2 (COX-2) inhibitors in the management of SLE is as yet unknown. These drugs have not been tested in patients with SLE, and their effect on kidney function is unclear.

Most authorities recommend regular ophthalmologic assessments (every 6–12 months) to detect early retinal toxicity of antimalarial agents. The incidence of this side effect with hydroxychloroquine is low (32).

In patients receiving long-term glucocorticoid therapy, electrolyte, glucose, and lipid levels should be monitored to identify metabolic complications. They should also undergo bone densitometry (dual x-ray absorptiometry scanning) to identify osteoporosis and to monitor its response to treatment (33). Patients with hip, knee, or shoulder pain suggestive of avascular necrosis of bone should undergo radiography of the appropriate site. If radiographs are not informative, magnetic resonance imaging should be considered to detect avascular necrosis at an early stage, to allow for early intervention such as core decompression (34). Patients taking steroids are compromised hosts in whom signs of infection may be masked. Therefore, one should always be vigilant for infectious complications and infection with atypical organisms (13).

Patients receiving immunosuppressive/cytotoxic medications (methotrexate, azathioprine, cyclophosphamide) should be monitored carefully for evidence of hematologic toxicity, liver and renal toxicity, and the possibility of infection (Table 7). At times it is difficult to distinguish between manifestations of active SLE and side effects of medications. While cytopenias may represent drug toxicity, they may also result from active inflammation for which drug doses should be increased. If the cytopenias occur in association with serologic abnormalities, it is more likely that the SLE is active than that this is a result of drug toxicity. Likewise, fever may represent active lupus or infection. If there are other clinical or laboratory manifestations of active disease, the diagnosis is facilitated. However, since infection is more likely to develop in the context of active SLE, the differentiation may become difficult (35). Patients with SLE are often treated for infection and active disease simultaneously until the results of cultures are obtained.

Table 9. Treatment of mild systemic lupus erythematosus

1. Patient education
   a. Realistic expectations
   b. Avoid extensive ultraviolet light exposure
   c. Avoid exhaustion
   d. Identify symptoms and signs of flare
   e. Comply with recommended treatment
   f. Keep medical appointments
2. Analgesic treatment as needed
3. Nonsteroidal antiinflammatory drug treatment as needed
   (Cautions regarding side effects: gastric erosions/ulcers/bleeding, decrease in renal function, increase in liver enzyme levels, aseptic meningitis)
4. Topical glucocorticoid treatment for rash
   (Caution: avoid using high-potency preparations on the face for more than several days)
5. Topical sunscreens (minimum sun protection factor of 15 recommended)
6. Rest when patient senses a flare beginning
7. Antimalarial drug treatment (hydroxychloroquine is most frequently used, at 200–400 mg/day)
   (Caution: patient will need ophthalmologic examination at least annually if therapy is continued longer than 6 months)*
8. Low-dose glucocorticoid therapy (not to exceed 10 mg of prednisone or equivalent daily)*

* Referral to specialist is recommended if these interventions are required.

Management

General considerations. All SLE patients need education, counseling, and support due to the complexity and unpredictability of the disease process. Patient education programs for SLE patients and their families are designed to provide information, knowledge, and social support with an emphasis on enhancing self-management skills (36). Such support may also come from local organizations such as the Lupus Foundation of America, Lupus Canada, and the Arthritis Foundation. Patients need advice regarding physical measures, including minimizing sun exposure, using sunscreens, and exercising regularly. Diet management for prevention of obesity, osteoporosis, and hyperlipidemia is of particular importance. Routine health maintenance, including regular gynecologic assessments, dental care, and ophthalmologic examinations (especially for patients taking glucocorticoids or antimalarial drugs), is very important in this chronic systemic disease. Preventive measures such as immunizations (e.g., hepatitis B, *Haemophilus influenzae,* Pneumovax, and influenza) or the use of hormone replacement therapy should be

coordinated with the SLE care expert. Since cardiovascular disease is a major cause of long-term morbidity and mortality among patients with SLE (13,14), strategies to identify and treat risk factors are essential.

Treatment of mild SLE (Table 9). *Topical sunscreens.* Patients with SLE may experience cutaneous or systemic disease flares when exposed to ultraviolet light (37); these patients should be encouraged to protect themselves from such exposure. Wearing protective clothing, applying sunscreens with a sun protection factor of at least 15 whenever outdoors, and avoidance of sunbathing should be emphasized.

Topical glucocorticoid preparations. Creams, ointments, and other vehicles are used to apply glucocorticoids to affected areas. Intermediate- rather than high-strength topical steroids should be used on steroid-sensitive areas that are prone to atrophy, such as the face. Cyclical application of more potent glucocorticoids may be required (38).

NSAIDs. NSAIDs are sometimes helpful for control of fever, arthritis, and mild serositis. However, salicylate-induced hepatitis has been noted among patients with SLE, and aseptic meningitis has developed in SLE patients given ibuprofen (31). Other NSAIDs may cause similar reactions. NSAIDs may cause or aggravate hypertension, peripheral edema, and renal impairment in SLE patients. Whether the COX-2 inhibitors will have a better safety profile among patients with SLE remains unknown.

Antimalarial agents (e.g., hydroxychloroquine). Antimalarial agents are useful for skin and joint manifestations of SLE, for preventing flares, and for other constitutional symptoms of the disease (32,38–40). They may also reduce fatigue and decrease levels of low-density lipoproteins.

Oral glucocorticoids. Patients with mild SLE usually do not need systemic glucocorticoid treatment. However, some patients do not have an acceptable quality of life unless treated with low-dose daily or alternate-day glucocorticoids (≤10 mg of prednisone/day or equivalent). Given the significant toxicity of glucocorticoids, initiation of therapy with these agents, along with strategies to minimize steroid side effects (e.g., consideration of steroid-sparing agents, and prevention of osteoporosis and infections), is an indication for referral.

Treatment of serious, life-threatening, or organ-threatening SLE (Table 10). Organ involvement may lead to irreversible damage in the affected organ. For example, patients with lupus nephritis may develop rapidly progressive renal failure. Patients with cardiac involvement may develop heart failure, valvular insufficiency, or pericardial tamponade. Severe anemia or thrombocytopenia may be life threatening. These patients require care by a specialist skilled in the management of SLE.

Table 10. Examples of organ- or life-threatening disease manifestations

Cardiac	Pulmonary
Coronary vasculitis/vasculopathy	Pulmonary hypertension
Libman-Sacks endocarditis	Pulmonary hemorrhage
Myocarditis	Pneumonitis
Pericardial tamponade	Emboli/infarcts
Malignant hypertension	Shrinking lung
	Interstitial fibrosis
Hematologic	Gastrointestinal
Hemolytic anemia	Mesenteric vasculitis
Neutropenia (white blood cells $<1{,}000/mm^3$)	Pancreatitis
Thrombocytopenia ($<50{,}000/mm^3$)	Renal
Thrombotic thrombocytopenic purpura	Persistent nephritis
Thrombosis (venous or arterial)	Rapidly progressive glomerulonephritis
	Nephrotic syndrome
Neurologic	Skin
Seizures	Vasculitis
Acute confusional state	Diffuse severe rash, with ulceration or blistering
Coma	
Stroke	Constitutional
Transverse myelopathy	High fever (prostration) in the absence of infection
Mononeuritis, polyneuritis	
Optic neuritis	
Psychosis	
Demyelinating syndrome	
Muscle	
Myositis	

High-dose glucocorticoids (1–8,16,24,41–43). Glucocorticoids are used for refractory manifestations of SLE, as well as for severe organ-threatening disease. High-dose, daily glucocorticoid therapy (40–60 mg/day of prednisone) improves survival among patients with severe forms of SLE nephritis (41), but is associated with virtually universal undesirable side effects. The dosage and mode of administration of glucocorticoids will depend on the nature and severity of the condition. Thus, refractory serositis may require relatively low doses, up to 20 mg per day of prednisone or equivalent. However, depending on the individual's sensitivity to steroids, that dosage may cause significant side effects. The treatment of active SLE nephritis, cerebritis, or thrombocytopenia may require high doses of 40–60 mg of prednisone per day, or intravenous pulses of up to 1 gm of methylprednisolone per day for 3 consecutive days. Studies of monthly high-dose intravenous methylprednisolone (in

addition to daily oral glucocorticoids) have shown a positive effect on severe SLE nephritis, although the therapy is not as effective as intermittent intravenous cyclophosphamide added to oral glucocorticoids (44). The exact dosage will depend on the sensitivity of the individual, and the exact nature of his or her disease.

Immunosuppressive/cytotoxic agents (1–9,16,24, 42–48). A number of immunosuppressive/cytotoxic medications have been used to treat SLE. These include azathioprine, cyclophosphamide, methotrexate, chlorambucil, cyclosporine, and nitrogen mustard. The choice of drug will depend on the nature and severity of the condition, as well as individual preference. For example, for patients with particularly severe arthritis, methotrexate may be preferred as the first cytotoxic medication, whereas for SLE nephritis, azathioprine or cyclophosphamide may be chosen first. In a series of long-term studies (>20 years of followup) in patients with SLE nephritis, treatment with glucocorticoids plus cyclophosphamide for >2 years appears to be superior to glucocorticoids plus azathioprine, and both seem superior to glucocorticoids alone in preventing renal failure in these patients (16,24,42,43). There is evidence that cytotoxic agents plus low-dose steroids prevent scarring in the kidney better than do glucocorticoids alone (21). However, some patients with severe disease (renal or extrarenal) respond well over both the short term and the long term to glucocorticoids alone, or they require only a few months of treatment with cytotoxic agents plus glucocorticoids to achieve long-term improvement. Nonrenal manifestations of SLE that may respond to cytotoxic drugs if glucocorticoid treatment is unsuccessful or is not tolerated include cytopenia, CNS manifestations, pulmonary hemorrhage, and vasculitis (1–8,45,46). There are several reports of SLE arthritis or nephritis responding to methotrexate (47,48). Variations in responses to therapy, in addition to the considerable toxicity of all of the regimens, necessitate expert management.

Management of severe SLE without renal involvement. Additional treatment approaches have been used in certain circumstances among patients with SLE. In a controlled trial, intravenous gamma globulin was not superior to daily high-dose glucocorticoid therapy among patients with idiopathic thrombocytopenic purpura (49). However, intravenous gamma globulin can produce short-term improvement in patients with SLE-related immune thrombocytopenia or hemolytic anemia, as can splenectomy, danazol, cyclosporine, and various chemotherapy regimens (50–52). Plasmapheresis has not provided added benefit to glucocorticoids plus cyclophosphamide in controlled trials of SLE nephritis (53,54). However, apheresis has been used for cytopenias, cryoglobulinemia, and occasionally for CNS disease. Plasmapheresis or plasma exchange is often life-saving in SLE-associated thrombotic thrombocytopenic purpura (55). Cyclosporin A has been used to treat severe disease (52); however, its low efficacy-to-toxicity ratio requires that it be administered by a physician who is expert in its use. Dapsone has been used primarily for refractory skin lesions. Retinoid derivatives have also been used for resistant skin lesions (38). Patients who have had thrombotic events in the setting of SLE usually require anticoagulation rather than immunosuppression (56).

End-stage renal disease. In spite of optimal therapy, in some cases SLE advances to end-stage renal disease, necessitating dialysis and/or renal transplantation. The rate of recurrence of SLE in transplanted kidneys is ~6%, and rejection rates may be somewhat higher than those in the general population of patients who have undergone renal transplantation (57). However, most patients do well, and choosing this modality rather than vigorous immunosuppressive treatment should be considered by both patient and physician.

Investigational treatments. Several experimental interventions are being studied in SLE. Some, such as DHEA, may have a steroid-sparing effect in individuals with mild disease (58). Others, such as new lymphocyte-specific immunosuppressive strategies, tolerogens, and biologic modifiers that prevent B cell activation and autoantibody production, may be useful in the treatment of severe SLE. All such interventions should be supervised by specialists with experience in their use.

Summary

SLE is a complex disorder with variable presentations, course, and prognosis. Since its prevalence is only 1/1,000, most primary care physicians and general internists will not have sufficient experience in the management of moderate-to-severe life-threatening disease. The major tasks of the primary care physician in the diagnosis and management of patients with SLE include early diagnosis, appropriate referral, monitoring patients with mild, stable disease, and collaboration with a specialist in the management of severe disease. Guidelines for the initial evaluation, reasons for referral, and management of mild and severe SLE are provided.

ACKNOWLEDGMENTS

The Ad Hoc Committee acknowledges the contributions of Dr. Suzanne Guilliam (Portland, OR), Dr. Gordon

Hardacre (Toronto, Ontario, Canada), Dr. Laura Robbins (New York, NY), and the members of the American College of Rheumatology Board of Directors for their helpful contributions to the manuscript.

REFERENCES

1. Lahita RG, editor. Systemic lupus erythematosus. 3rd ed. San Diego: Academic Press; 1998.
2. Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 5th ed. Baltimore: Williams & Wilkins; 1997.
3. Schur P, editor. The clinical management of systemic lupus erythematosus. 2nd ed. Philadelphia: Lippincott; 1996.
4. Klippel J, editor. Primer on the rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997.
5. Klippel JH, Dieppe PA, editors. Rheumatology. London: Mosby; 1998.
6. Koopman WJ, editor. Arthritis and allied conditions. 13th ed. Baltimore: Williams & Wilkins; 1997.
7. Kelley WN, Harris ED, Ruddy S, Sledge CB, editors. Textbook of rheumatology. 5th ed. Philadelphia: WB Saunders; 1997.
8. Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. Oxford textbook of rheumatology. Oxford: Oxford University Press; 1997.
9. 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;25:1271–7.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
11. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, 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.
12. Stoll T, Seifert B, Isenberg DA. SLICC/ACR damage index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. Br J Rheumatol 1996;35:248–54.
13. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus: results from a single centre. I. Causes of death. J Rheumatol 1995;22:1259–64.
14. Urowitz MB, Bookman AAM, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221–5.
15. Gladman DD. Prognosis and treatment of systemic lupus erythematosus. Curr Opin Rheumatol 1996;8:430–7.
16. Boumpas DT, Fessler BJ, Austin HA III, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 2. Dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. Ann Intern Med 1995;123:42–53.
17. Esdaile JM, Joseph L, Mackenzie T, Kashgarian M, Hayslett JP. The benefit of early treatment with immunosuppressive agents in lupus nephritis. J Rheumatol 1994;21:2046–51.
18. Weinstein A, Bordwell B, Stone B, Tibbetts C, Rothfield NF. Antibodies to native DNA and serum complement (C3) levels: application to diagnosis and classification of systemic lupus erythematosus. Am J Med 1983;174:206–16.
19. Perez-Gutthann S, Petri M, Hochberg MC. Comparison of different methods of classifying patients with systemic lupus erythematosus. J Rheumatol 1991;18:1176–9.
20. Shiel WC Jr, Jason M. The diagnostic associations of patients with antinuclear antibodies referred to a community rheumatologist. J Rheumatol 1989;16:782–5.
21. Hahn BH. Mechanisms of disease: antibodies to DNA. N Engl J Med 1998;338:1359–68.
22. Calvo-Alén J, Bastian HM, Straaton KV, Burgard SL, Mikhail IS, Alarcón GS. Identification of patient subsets among those presumptively diagnosed with, referred, and/or followed up for systemic lupus erythematosus at a large tertiary care center. Arthritis Rheum 1995;38:1475–84.
23. Kalunian KC. Definition, classification, activity and damage indices. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 5th ed. Baltimore: Williams and Wilkins; 1997. p. 19–30.
24. Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1. Renal, neuropsychiatric, cardiovascular, pulmonary and hematologic disease. Ann Intern Med 1995;122:940–50.
25. Ter Borg EJ, Horst G, Hummel EJ, Limburg PC, Kallenberg CGM. Measurement of increases in anti–double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus: a long-term, prospective study. Arthritis Rheum 1990;33:634–43.
26. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus: a prospective cohort study. Arthritis Rheum 1991;34:937–44.
27. Bootsma H, Spronk P, Derksen R, de Boer G, Wolters Dicke H, Hermans J, et al. Prevention of relapses in systemic lupus erythematosus. Lancet 1995;345:1595–9.
28. Walz-Leblanc B, Gladman DD, Urowitz MB, Goodman PJ. Serologically active clinically quiescent SLE. J Rheumatol 1994; 21:2239–41.
29. Esdaile JM. Current role of renal biopsy in SLE. Baillieres Clin Rheumatol 1998;12:433–8.
30. Agus B, Nelson J, Kramer N, Mahal SS, Rosenstein ED. Acute central nervous system symptoms caused by ibuprofen in connective tissue disease. J Rheumatol 1990;17:1094–6.
31. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs: Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338:727–34.
32. Wallace DJ. Antimalarial agents and lupus. Rheum Dis Clin North Am 1994;20:243–63.
33. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 1996;39: 1791–801.
34. Mont MA, Glueck CJ, Pacheco IH, Wang P, Hungerford DS, Petri M. Risk factors for osteonecrosis in systemic lupus erythematosus. J Rheumatol 1997;24:654–62.
35. Watanabe Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in SLE: a review of hospitalized patients. J Rheumatol 1991;18:1180–4.
36. Robbins L. Patient education. In: Klippel J, Weyand C, Wortmann R, editors. Primer on the rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997. p. 416–8.
37. Wysenbeek AJ, Block DA, Fries JF. Prevalence and expression of photosensitivity in systemic lupus erythematosus. Ann Rheum Dis 1989;48:461–3.
38. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky SK, et al. Guidelines of care for cutaneous lupus erythematosus. J Am Acad Dermatol 1996;34:830–6.
39. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 1991; 324:150–4.

40. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. Am J Med 1994;96:254–9.
41. Pollak VE, Pirani CL, Kark RM. Effect of large doses of prednisone on the renal lesions and life span of patients with lupus glomerulonephritis. J Lab Clin Med 1961;57:495–511.
42. Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone versus prednisone alone in the treatment of systemic lupus erythematosus: a report of a prospective, controlled trial in 24 patients. Ann Intern Med 1975;85:597–605.
43. Steinberg AD, Steinberg SC. Long term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum 1991;34:945–50.
44. Gourley MF, Austin HA III, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: a randomized, controlled trial. Ann Intern Med 1996;125:549–57.
45. Boumpas DT, Barez S, Klippel JH, Balow JE. Intermittent cyclophosphamide for the treatment of thrombocytopenia in systemic lupus erythematosus. Ann Intern Med 1990;112:674–7.
46. Boumpas DR, Yamada H, Patronas NJ, Scott D, Klippel JH, Balow JE. Pulse cyclophosphamide for severe neuropsychiatric lupus. QJM 1991;81:975–84.
47. Walz-Leblanc B, Urowitz MB, Gladman DD. Methotrexate in SLE. J Rheumatol 1994;21:836–8.
48. Wilson K, Abeles M. A 2 year, open ended trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1994;21:1674–7.
49. Jacobs P, Woods L. The comparison of gammaglobulin to steroids in treating adult immune thrombocytopenia: an interim analysis. Blut 1989;59:92–5.
50. West SG, Johnson SC. Danazol for the treatment of refractory autoimmune thrombocytopenia in systemic lupus erythematosus. Ann Intern Med 1988;108:703–6.
51. Coon WW. Splenectomy for cytopenias associated with systemic lupus erythematosus. Am J Surg 1988;155:391–4.
52. Tokuda M, Kurata N, Mizoguchi A, Inoh M, Seto K, Kinashi M, et al. Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. Arthritis Rheum 1994;4:551–8.
53. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. N Engl J Med 1992;326:1373–9.
54. Euler HH, Schwab UM, Schroeder JO, Hasford J. The Lupus Plasmapheresis Study Group; rationale and updated interim report. Artif Organs 1996;20:356–9.
55. Rund D, Schaap T, Gillis S. Intensive plasmapheresis for severe thrombotic thrombocytopenic purpura: long-term clinical outcome. J Clin Apheresis 1997;12:194–5.
56. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid antibody syndrome. N Engl J Med 1995;332:993–7.
57. Stone JH, Millward CL, Olson JL, Amend WJC, Criswell LA. Frequency of recurrent lupus nephritis among ninety-seven renal transplant patients during the cyclosporine era. Arthritis Rheum 1998;41:678–86.
58. Van Vollenhoven RF, Engleman EG, McGuire JL. Dehydroepiandrosterone in systemic lupus erythematosus: results of a double-blind, placebo-controlled, randomized clinical trial. Arthritis Rheum 1995;38:1826–31.